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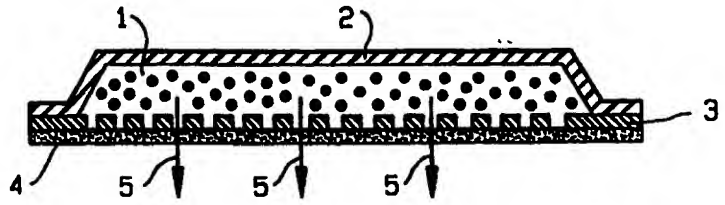
(54) Title: COMPOSITIONS, METHODS AND DEVICES FOR THE TRANSDERMAL DELIVERY OF DRUGS

(57) Abstract




The present invention is directed to compositions, and methods for the delivery of drugs. Devices for the transdermal delivery of drugs are also provided. Specifically, the present invention relates to hydrogel compositions comprising water and a base mixture, in which the base mixture comprises: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride. The compositions may further comprise pectin, glycolic, alcoholic or oil-based additives, a coloring, fragrance, or other pharmaceutically acceptable additive. The compositions may further comprise substituted ureas of the formula R-NH-CO-$NH_2$ such as butylurea. The compositions may further comprise drugs such as hormones selected from progesterone, progestin, estrogen and testosterone. Methods for the treatment of disorders responsive to hormone therapy are also provided. The figure is a cross-sectional view of a membrane-moderated transdermal drug delivery system.

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# COMPOSITIONS, METHODS AND DEVICES FOR THE TRANSDERMAL DELIVERY OF DRUGS

## 1. INTRODUCTION

The present invention relates to compositions for the transdermal delivery of hormones comprising a hydrogel-forming base mixture and a skin permeation enhancer. Methods for the treatment of disorders responsive to the administration of hormones are also provided. The present invention further relates to devices for the transdermal delivery of drugs.

## 2. BACKGROUND

A recent trend in the pharmaceutical industry has been the development of new drug delivery systems for both old and new drugs. Much of the current research in drug delivery technology is aimed at developing formulations and devices that improve the therapeutic effectiveness of drugs over conventional means of administration by controlling the rate, time and place of release of drugs in the body.

Conventional dosage types include sublingual (under the tongue), oral (capsules, tablets, liquids), injectable, nasal and parenteral (suppository and non-oral) forms. While oral dosage forms comprise a substantial majority of all present dosage forms and offer ease of administration and low cost-per-use, they can suffer from inconvenient dosing intervals, side effects and reduced efficacy. Conventional dosage forms have disadvantages in certain patients, including unpredictable blood levels, difficult or uncomfortable administration and poor compliance. In order to maintain optimum blood levels, some conventional forms of drug delivery require frequent doses which can be difficult to remember or understand, particularly for the elderly patient. Failure to comply with a recommended drug regimen can endanger a patient's health.

Controlled drug delivery systems have been introduced within the last decade to eliminate or reduce the limitations of conventional dosage forms. One type of controlled delivery is transdermal delivery, which involves delivery of a therapeutic agent through the skin for distribution within the body by the circulation of the blood. Transdermal delivery can be compared to continuous, controlled intravenous delivery of

a drug using the skin as a port of entry instead of an intravenous needle. The therapeutic agent passes through the outer layers of the skin, diffuses into the capillaries, or tiny blood vessels in the skin, and then is transported into the main circulatory system.

Examples of drugs which have successfully been delivered transdermally include scopolamine for the treatment of motion sickness, nitroglycerin for the treatment of angina, estrogen and combined estrogen/progestogen for menopausal symptoms and osteoporosis, isosorbide dinitrate for angina, clonidine for hypertension, nicotine for smoking cessation, fentanyl for pain management and testosterone for male hypogonadism.

The hormone progesterone is used in the treatment of premenstrual syndrome, menopausal hormone replacement therapy (in combination with estrogen), infertility and a variety of gynecological conditions. In ovulating females, progesterone is chiefly produced by the corpus luteum of the ovary with smaller amounts made in the adrenal cortex in both sexes, and in the testes of males. Within the cytoplasm of cells are minute organelles called the mitochondria, which convert cholesterol to pregnenolone. Pregnenolone, on being transferred to the cytoplasm, is converted to progesterone or DHEA depending on cell type and body needs. With the development of the corpus luteum at ovulation, the ovarian production of progesterone rapidly rises from 2-3 mg per day to an average of 22 mg per day, peak production being as high as 30 mg per day, a week or so after ovulation. After 10 to 12 days, if fertilization does not occur, ovarian production of progesterone falls dramatically. It is the sudden decline in progesterone levels which triggers the shedding of the secretory endometrium leading to a renewal of the entire menstrual cycle. During pregnancy, production of progesterone is taken over by the placenta which secretes an ever increasing supply, reaching 300-400 mg per day during the third trimester.

Progesterone as it is secreted into the blood stream is bound within a water soluble protein (termed cortisol binding globulin; CBG), being the same globulin used by cortisol for passage through the plasma. Only a small portion of progesterone (2-10%) circulates unbound through the plasma. A molecular framework of progesterone, having been derived from cholesterol, is very similar to the cholesterol molecule, and

like cholesterol is fat soluble. As such, it would not be soluble in the watery plasma were it not for the CBG protein carrier. In close proximity to a cell, progesterone is freed from the CBG and passes easily through cell membranes into the cell cytoplasm where, if it encounters and binds to an accessible receptor, forms an activated complex which migrates into the cell nucleus for binding with an accessible DNA segment (genome) resulting in the formation of a specific RNA by which the cellular effects of progesterone are brought into being. If the progesterone passes into a cell lacking an appropriate progesterone receptor, it will simply pass on through and out the cell again.

Eventually, progesterone molecules are carried by the blood through the liver where they are inactivated and disposed of by the bile and urine. Progesterone, in addition to its own intrinsic hormonal effect is an important precursor in the biosynthesis of various hormones. Specialized cells in key organs throughout the body use progesterone to synthesize other hormones as needed, specifically the adrenal corticosteroids, estrogen and testosterone. This aspect of progesterone distinguishes it from most other hormones which are at a metabolic endpoint. This means they are unable to be used in further metabolic functions, except to be metabolized for excretion. More specifically, the various synthetic analogues of progesterone now being promoted heavily have undergone molecular alterations at unusual positions that inhibit further metabolism, and thus are not subject to feedback control by the body to prevent excessive or improperly prolonged activity. Unfortunately, these molecular alterations carry a heavy burden of potential undesirable side effects.

The transdermal delivery of progesterone has been reported. However, due to the large size of the progesterone molecule, efforts to transdermally deliver progesterone in therapeutically effective amounts have often been unsuccessful. Progesterone is known to be metabolized within the skin by the 5-α-reductase enzyme which converts it to inactive 5-α-dihydroxyprogesterone (R. Sitruk-Ware, 1995, "Transdermal Application of Steroid Hormones for Contraception," J. Steroid Biochem. Molec. Biol. 53 (1-6):247-251). Thus, relatively high, multiple doses are required to elicit the desired progestational effect. The desired goal of transdermal delivery of progesterone is to be able to maintain consistent serum levels of progesterone at relatively low dosage levels without requiring multiple dosing.

Low rates of transdermal delivery of progesterone have been reported by various researchers. For example, Guy et al. (1987, "Kinetics of Drug Absorption Across Human Skin In Vivo," Pharmacol. Skin 1:70-76), disclose that about 1.2 $\mu g/cm^2$ penetrated in a 24-hour period, when the drug was applied as a thin film on the skin *in vivo*. Barry and Bennett, (1987, "Effect of Penetration Enhancers on the Permeation of Mannitol, Hydrocortisone, and Progesterone Through Human Skin," J. Pharm. Pharmacol. 39:535-546), report a rate of 0.477 $\mu g/cm^2$/ hour *in vitro* through excised human skin. Both Guy et al. and Barry and Bennett measured penetration through the skin after progesterone was applied in an acetone solution, the solvent was allowed to evaporate, and the skin surface was hydrated, either by occlusion or by application of a small amount of water. Barry and Bennett reported higher rates of transdermal penetration of progesterone when penetration enhancers were applied to the skin following application of the acetone/progesterone solution and evaporation of the solvent. Rates of 11.4 (+/- 4.6) and 12.4 (+/- 4.4) $\mu g/cm^2$/hour, respectively, were observed after application of 2-pyrrolidone and N-methylformamide permeation enhancers. However, neither the methods nor the solvent vehicles for application of progesterone to the skin disclosed by these references are appropriate or practical for use in a transdermal patch delivery system, for number of reasons. Application of acetone to the skin commonly results in skin irritation, an effect that may also be encountered with 2-pyrrolidone and N-methylformamide. Further, permeation enhancers such as 2-pyrrolidone and N-methylformamide may impose health risks. Also, the volatile solvent carriers disclosed by these references can be difficult and impractical to incorporate into a patch system.

The transdermal delivery of progesterone, progestins, estrogens and testosterone from gel-like matrices has been reported. R. Sitruk-Ware (1988, "Innovative Technology for Hormonal Replacement Therapy," Maturitas, 10:79-81) discloses a progesterone cream for use as a topical therapy in benign breast diseases. R. Sitruk-Ware (1989, "Transdermal Delivery of Steroids," Contraception 39, (1):1-20) discloses that only small amounts of progesterone can be obtained in plasma via skin penetration, but when applied on the breast, high amounts of progesterone can be obtained in the breast tissue. A five-fold increase in progesterone concentration was demonstrated in

breast tissue of women treated topically with the steroid dissolved in an alcohol/water gel.

Compounds that act as permeation enhancers have been added to transdermal drug delivery systems for a number of drugs, including progesterone. Pfister and Hsieh (1990, in "Permeation Enhancers with Transdermal Drug Delivery Systems: Part II: System Design Considerations," Pharmaceutical Technology, October 1990: 55-60), disclose a wide variety of permeation enhancers. For example, isopropyl palmitate and isopropyl myristate are disclosed as cosolvents to enhance the solubility of nitroglycerin in a polymer matrix-type transdermal system, which in turn optimizes the release of the drug from the system. Similarly, ethanol is disclosed as enhancing the solubility of 17-β-estradiol in the reservoir compartment of a transdermal drug delivery device. Other skin penetration enhancers are disclosed, including stearyl alcohol, glycerol, 2-pyrrolidone, urea, propylene glycol, oleic acid, and palmitic acid. D.R. Friend (1990, "Transdermal Delivery of Contraceptives", Critical Reviews in Therapeutic Drug Carrier Systems 7 (2):149-186), discloses dimethyl sulfoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 2-pyrrolidone-5-carboxylic acid, N,N-dimethyl-m-toluamide, urea, ethyl acetate, 1-dodecylazacycloheptan-2-one (azone), oleic acid and ethanol as permeation enhancers. Butylurea has also been disclosed as a permeation enhancer. For example, U.S. Patent No. 5,128,376 discloses a method for percutaneous administration of a drug from a mixture of an adjuvant, a solvent and a diol/triol moderator, wherein the solvent, which enhances permeation, may be a substituted urea such as butylurea. U.S. Patent No. 4,863,952 discloses an improved method of drug administration using a mixture comprising pyrrolidone carboxylic acid esters as percutaneous promoters, and optionally, substituted ureas such as butylurea. S.K. Han et al. (1991, "Percutaneous Absorption-Enhancing Activity of Urea Derivatives," Arch. Pharm. Res. 14(1):12-18) disclose the use of urea derivatives, including butylurea, to enhance the percutaneous absorption of salicylic acid and sodium salicylate from a vaseline base.

Hydrogels are well known in the art as vehicles for the controlled release of drugs. N.A. Peppas, ed., "Hydrogels in Medicine and Pharmacy," CRC Press, Inc.

(1987) Vol. II, discloses the use of water soluble cellulose ethers such as methylcellulose for controlled release drug delivery systems. Volume III of the same publication discloses the release of progesterone from rod-shaped monolithic hydrogel devices.

U.S. Patent Nos. 5,344,655 and 5,254,338 disclose that hydrogel bases containing water soluble polymers such as cellulose derivatives are known in the art for delivery of drugs through the skin. U.S. Patent No. 4,693,887 discloses hydrogel compositions for the controlled release of contraceptives such as progesterone. The hydrogels are blends of either N-vinyl lactam or a copolymer of N-vinyl lactam and may further comprise spermicides such as urea. U.S. Patent No. 5,405,366 discloses an adhesive hydrogel comprising an aqueous mixture of a radiation crosslinkable water-soluble polymer such as a polymer of N-vinyl-2-pyrrolidone and ethylene oxide and a humectant such as propylene glycol which may be used in a transdermal drug delivery system. The hydrogel may also contain preservatives such as propyl paraben and methyl paraben. U.S. Patent No. 4,593,053 discloses a skin-compatible pressure-sensitive adhesive hydrogel comprising polyvinyl pyrrolidone and polyvinyl alcohol, a polar plasticizer or humectant such as propylene glycol, water and a drug. The composition may also contain cellulose derivatives to increase strength and guar gum to increase tackiness.

The transdermal delivery of progesterone, progestins, estrogens and testosterone from hydrogel matrices comprising permeation enhancers is also known. For example, U.S. Patent No. 5,030,629 discloses transdermal formulations containing progesterone, ethanol, saline and an imidazoline penetration enhancer. Dosage forms of the formulations for application to the skin include gels, which may comprise inert carriers such as propylene glycol, urea and methylcellulose. U.S. Patent No. 5,362,497 discloses compositions for transdermal delivery of, *inter alia*, androgens such as testosterone and estrogens such as estradiol comprising water- and fat-soluble absorption enhancers, and a water-absorbent resin such as a vinyl acetate-acrylic acid ester copolymer that swells to form a hydrogel upon contact with water. U.S. Patent No. 5,064,654 discloses a transdermal drug formulation comprising a drug such as progesterone or estradiol, water and ethanol. The formulation may also contain an

adhesive or gelling agent such as pectin, guar gum or methyl cellulose. U.S. Patent No. 4,942,158 discloses a composition comprising a combination of isopropyl alcohol and isobutyl alcohol to enhance the transdermal penetration of steroids such as estradiol, or a combination of estradiol with a progestogen. The composition may also include water and a gelling agent such as methyl cellulose. U.S. Patent No. 4,865,848 discloses compositions for enhancing the transdermal delivery of drugs, including progesterone, comprising sucrose esters as penetration enhancers. Preferably, the permeation enhancer and the drug are dispersed in a matrix which may be a gel or a hydrophilic polymer.

Despite their advantages, conventional transdermal delivery systems have been limited due to barrier properties of the stratum corneum, the skin's protective outer layer. Large, high molecular weight drugs such as progesterone are difficult to deliver through the skin in effective amounts. In general, the skin is highly resistant to permeation by chemicals, including drugs. Although the skin is only a few millimeters thick, the stratum corneum serves as a highly protective barrier against physical, chemical and bacterial penetration. This barrier primarily consists of dead skin cells bound together by certain fatty (lipid) materials. Generally, only drugs that are effective in the body at very low concentrations or that have particular physical properties have been successfully delivered through the skin in therapeutically effective amounts. High molecular weight drugs and drugs which are either charged or highly polar remain difficult to administer transdermally.

Natural progesterone, which is the form of progesterone that is produced by the body, has been administered in oral, injectable and suppository forms. The disadvantages of injectable and suppository forms are obvious: they are burdensome to administer. The disadvantage of oral forms is that they are short acting, and to maintain adequate blood levels, they have to be dosed throughout the day. The bulk of orally administered progesterone is metabolized by the digestive system and excreted before it can be used by the body. In fact, progesterone, whether administered orally, vaginally or rectally, has a half life in the body of only about 2.2 hours. Therefore, much larger amounts than the body actually requires must be dosed to maintain effective blood levels.

To address the problems associated with conventional means of administration of natural progesterone, a variety of synthetic forms, known as progestins, have been developed. Progestins fall primarily into two categories. The first group, pregnanes, is derived from 17-α-acetoxy progesterone. A classic example is medroxy progesterone acetate (Provera). With an increased affinity for progesterone receptors, these compounds have marked progestational activity. They possess anti-estrogenic anti-gonadotropic, and no significant androgenic properties. A second group, estranes, derived from 17-α-ethinyl-1-nortestosterone, includes norethindrone acetate (aygestin). Besides progestational activity, these compounds have marked anti-estrogenic, some anabolic, moderate androgenic, and as a result, pronounced anti-gonadotropic activities.

Synthetic progesterones are 10-100 times more potent than natural progesterone, and thus are effective at much lower doses. However, synthetic progesterones (i.e., progestins) can cause many negative side effects, such as sudden or partial loss of vision, thrombophlebitis, pulmonary embolism, cerebral thrombosis, salt and fluid retention, epilepsy, migraine, asthma, cardiac or renal dysfunction, weight gain, rise in blood pressure, headaches, depression, decreased glucose tolerance leading to diabetes in predisposed individuals, acne, alopecia, hirsutism, decrease in T3 uptake and thyroid regulation.

A disadvantage of conventional patch systems is that many of them either incorporate drugs in an adhesive or require an adhesive to affix the patch to patient's skin. These adhesives can irritate the skin, causing patient non-compliance. Thus, there is a need for a non-adhesive transdermal delivery system that can deliver therapeutically effective amounts of hormones such as natural progesterone, progestins, estrogens and testosterone that will reduce or eliminate the skin irritation experienced by many patients using current adhesive patch transdermal delivery systems. This need is satisfied by a particular embodiment of the invention.

Although patches for the transdermal delivery of estrogen and testosterone are currently commercially available, progesterone can be obtained commercially at present only in oral, injectable and suppository forms. The transdermal delivery of natural progesterone from hydrogel matrix systems with potential for use in patches has been demonstrated; however, none of these systems has proven adequate for administration of

therapeutically effective amounts of progesterone. Accordingly, there is a need in the art for a matrix composition that can transdermally deliver and maintain therapeutically effective levels of hormones such as natural progesterone, progestins, estrogens and testosterone in the bloodstream from a convenient, reliable patch system.

Citation of the references hereinabove shall not be construed as an admission that such references are prior art to the present invention.

## 3. SUMMARY OF THE INVENTION

The present invention is directed to compositions for the transdermal delivery of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a combination thereof, said compositions comprising or alternatively consisting or consisting essentially of: (a) a hydrogel, or a base mixture that when combined with water forms a hydrogel; (b) a permeation enhancer selected from the group consisting of urea, hydroxyurea, or an alkylurea; and (c) a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a combination thereof. In a preferred embodiment, the hormone is natural progesterone. Natural progesterone is superior to synthetic forms of progesterone, known as progestins, in treating gynecological conditions. The invention also provides apparatuses for transdermal hormone delivery containing the compositions of the invention. Methods of transdermal drug delivery, and of treatment of disorders responsive to the administration of hormones, are also provided.

Transdermal delivery according to the invention offers significant advantages over conventional means of drug administration. It is a comfortable, convenient and noninvasive means of drug delivery. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and side effects such as gastrointestinal irritation and the like are eliminated. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of particular drugs.

Transdermal drug delivery according to the invention also helps provide patients with a drug's maximum therapeutic effect and decreases the risk of adverse side effects or diminished therapeutic effect due to excessive or insufficient blood concentrations. The therapeutic effect of a drug is typically achieved only when the drug is within a

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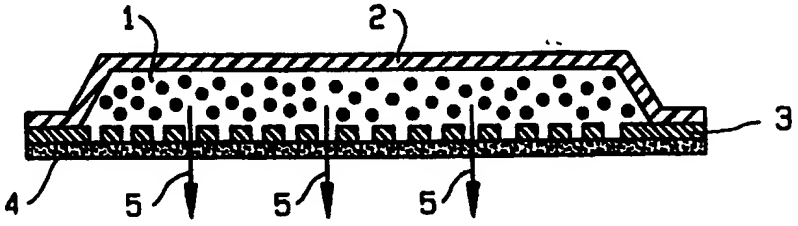


The present invention is directed to compositions, and methods for the delivery of drugs. Devices for the transdermal delivery of drugs are also provided. Specifically, the present invention relates to hydrogel compositions comprising water and a base mixture, in which the base mixture comprises: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride. The compositions may further comprise pectin, glycolic, alcoholic or oil-based additives, a coloring, fragrance, or other pharmaceutically acceptable additive. The compositions may further comprise substituted ureas of the formula R-NH-CO-$NH_2$ such as butylurea. The compositions may further comprise drugs such as hormones selected from progesterone, progestin, estrogen and testosterone. Methods for the treatment of disorders responsive to hormone therapy are also provided. The figure is a cross-sectional view of a membrane-moderated transdermal drug delivery system.

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## 2. BACKGROUND

A recent trend in the pharmaceutical industry has been the development of new drug delivery systems for both old and new drugs. Much of the current research in drug delivery technology is aimed at developing formulations and devices that improve the therapeutic effectiveness of drugs over conventional means of administration by controlling the rate, time and place of release of drugs in the body.

Conventional dosage types include sublingual (under the tongue), oral (capsules, tablets, liquids), injectable, nasal and parenteral (suppository and non-oral) forms. While oral dosage forms comprise a substantial majority of all present dosage forms and offer ease of administration and low cost-per-use, they can suffer from inconvenient dosing intervals, side effects and reduced efficacy. Conventional dosage forms have disadvantages in certain patients, including unpredictable blood levels, difficult or uncomfortable administration and poor compliance. In order to maintain optimum blood levels, some conventional forms of drug delivery require frequent doses which can be difficult to remember or understand, particularly for the elderly patient. Failure to comply with a recommended drug regimen can endanger a patient's health.

Controlled drug delivery systems have been introduced within the last decade to eliminate or reduce the limitations of conventional dosage forms. One type of controlled delivery is transdermal delivery, which involves delivery of a therapeutic agent through the skin for distribution within the body by the circulation of the blood. Transdermal delivery can be compared to continuous, controlled intravenous delivery of

a drug using the skin as a port of entry instead of an intravenous needle. The therapeutic agent passes through the outer layers of the skin, diffuses into the capillaries, or tiny blood vessels in the skin, and then is transported into the main circulatory system.

Examples of drugs which have successfully been delivered transdermally include scopolamine for the treatment of motion sickness, nitroglycerin for the treatment of angina, estrogen and combined estrogen/progestogen for menopausal symptoms and osteoporosis, isosorbide dinitrate for angina, clonidine for hypertension, nicotine for smoking cessation, fentanyl for pain management and testosterone for male hypogonadism.

The hormone progesterone is used in the treatment of premenstrual syndrome, menopausal hormone replacement therapy (in combination with estrogen), infertility and a variety of gynecological conditions. In ovulating females, progesterone is chiefly produced by the corpus luteum of the ovary with smaller amounts made in the adrenal cortex in both sexes, and in the testes of males. Within the cytoplasm of cells are minute organelles called the mitochondria, which convert cholesterol to pregnenolone. Pregnenolone, on being transferred to the cytoplasm, is converted to progesterone or DHEA depending on cell type and body needs. With the development of the corpus luteum at ovulation, the ovarian production of progesterone rapidly rises from 2-3 mg per day to an average of 22 mg per day, peak production being as high as 30 mg per day, a week or so after ovulation. After 10 to 12 days, if fertilization does not occur, ovarian production of progesterone falls dramatically. It is the sudden decline in progesterone levels which triggers the shedding of the secretory endometrium leading to a renewal of the entire menstrual cycle. During pregnancy, production of progesterone is taken over by the placenta which secretes an ever increasing supply, reaching 300-400 mg per day during the third trimester.

Progesterone as it is secreted into the blood stream is bound within a water soluble protein (termed cortisol binding globulin; CBG), being the same globulin used by cortisol for passage through the plasma. Only a small portion of progesterone (2-10%) circulates unbound through the plasma. A molecular framework of progesterone, having been derived from cholesterol, is very similar to the cholesterol molecule, and

like cholesterol is fat soluble. As such, it would not be soluble in the watery plasma were it not for the CBG protein carrier. In close proximity to a cell, progesterone is freed from the CBG and passes easily through cell membranes into the cell cytoplasm where, if it encounters and binds to an accessible receptor, forms an activated complex which migrates into the cell nucleus for binding with an accessible DNA segment (genome) resulting in the formation of a specific RNA by which the cellular effects of progesterone are brought into being. If the progesterone passes into a cell lacking an appropriate progesterone receptor, it will simply pass on through and out the cell again.

Eventually, progesterone molecules are carried by the blood through the liver where they are inactivated and disposed of by the bile and urine. Progesterone, in addition to its own intrinsic hormonal effect is an important precursor in the biosynthesis of various hormones. Specialized cells in key organs throughout the body use progesterone to synthesize other hormones as needed, specifically the adrenal corticosteroids, estrogen and testosterone. This aspect of progesterone distinguishes it from most other hormones which are at a metabolic endpoint. This means they are unable to be used in further metabolic functions, except to be metabolized for excretion. More specifically, the various synthetic analogues of progesterone now being promoted heavily have undergone molecular alterations at unusual positions that inhibit further metabolism, and thus are not subject to feedback control by the body to prevent excessive or improperly prolonged activity. Unfortunately, these molecular alterations carry a heavy burden of potential undesirable side effects.

The transdermal delivery of progesterone has been reported. However, due to the large size of the progesterone molecule, efforts to transdermally deliver progesterone in therapeutically effective amounts have often been unsuccessful. Progesterone is known to be metabolized within the skin by the 5-α-reductase enzyme which converts it to inactive 5-α-dihydroxyprogesterone (R. Sitruk-Ware, 1995, "Transdermal Application of Steroid Hormones for Contraception," J. Steroid Biochem. Molec. Biol. 53 (1-6):247-251). Thus, relatively high, multiple doses are required to elicit the desired progestational effect. The desired goal of transdermal delivery of progesterone is to be able to maintain consistent serum levels of progesterone at relatively low dosage levels without requiring multiple dosing.

Low rates of transdermal delivery of progesterone have been reported by various researchers. For example, Guy et al. (1987, "Kinetics of Drug Absorption Across Human Skin In Vivo," Pharmacol. Skin 1:70-76), disclose that about 1.2 $\mu g/cm^2$ penetrated in a 24-hour period, when the drug was applied as a thin film on the skin *in vivo*. Barry and Bennett, (1987, "Effect of Penetration Enhancers on the Permeation of Mannitol, Hydrocortisone, and Progesterone Through Human Skin," J. Pharm. Pharmacol. 39:535-546), report a rate of 0.477 $\mu g/cm^2$/ hour *in vitro* through excised human skin. Both Guy et al. and Barry and Bennett measured penetration through the skin after progesterone was applied in an acetone solution, the solvent was allowed to evaporate, and the skin surface was hydrated, either by occlusion or by application of a small amount of water. Barry and Bennett reported higher rates of transdermal penetration of progesterone when penetration enhancers were applied to the skin following application of the acetone/progesterone solution and evaporation of the solvent. Rates of 11.4 (+/- 4.6) and 12.4 (+/- 4.4) $\mu g/cm^2$/hour, respectively, were observed after application of 2-pyrrolidone and N-methylformamide permeation enhancers. However, neither the methods nor the solvent vehicles for application of progesterone to the skin disclosed by these references are appropriate or practical for use in a transdermal patch delivery system, for number of reasons. Application of acetone to the skin commonly results in skin irritation, an effect that may also be encountered with 2-pyrrolidone and N-methylformamide. Further, permeation enhancers such as 2-pyrrolidone and N-methylformamide may impose health risks. Also, the volatile solvent carriers disclosed by these references can be difficult and impractical to incorporate into a patch system.

The transdermal delivery of progesterone, progestins, estrogens and testosterone from gel-like matrices has been reported. R. Sitruk-Ware (1988, "Innovative Technology for Hormonal Replacement Therapy," Maturitas, 10:79-81) discloses a progesterone cream for use as a topical therapy in benign breast diseases. R. Sitruk-Ware (1989, "Transdermal Delivery of Steroids," Contraception 39, (1):1-20) discloses that only small amounts of progesterone can be obtained in plasma via skin penetration, but when applied on the breast, high amounts of progesterone can be obtained in the breast tissue. A five-fold increase in progesterone concentration was demonstrated in

breast tissue of women treated topically with the steroid dissolved in an alcohol/water gel.

Compounds that act as permeation enhancers have been added to transdermal drug delivery systems for a number of drugs, including progesterone. Pfister and Hsieh (1990, in "Permeation Enhancers with Transdermal Drug Delivery Systems: Part II: System Design Considerations," Pharmaceutical Technology, October 1990: 55-60), disclose a wide variety of permeation enhancers. For example, isopropyl palmitate and isopropyl myristate are disclosed as cosolvents to enhance the solubility of nitroglycerin in a polymer matrix-type transdermal system, which in turn optimizes the release of the drug from the system. Similarly, ethanol is disclosed as enhancing the solubility of 17-β-estradiol in the reservoir compartment of a transdermal drug delivery device. Other skin penetration enhancers are disclosed, including stearyl alcohol, glycerol, 2-pyrrolidone, urea, propylene glycol, oleic acid, and palmitic acid. D.R. Friend (1990, "Transdermal Delivery of Contraceptives", Critical Reviews in Therapeutic Drug Carrier Systems 7 (2):149-186), discloses dimethyl sulfoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 2-pyrrolidone-5-carboxylic acid, N,N-dimethyl-m-toluamide, urea, ethyl acetate, 1-dodecylazacycloheptan-2-one (azone), oleic acid and ethanol as permeation enhancers. Butylurea has also been disclosed as a permeation enhancer. For example, U.S. Patent No. 5,128,376 discloses a method for percutaneous administration of a drug from a mixture of an adjuvant, a solvent and a diol/triol moderator, wherein the solvent, which enhances permeation, may be a substituted urea such as butylurea. U.S. Patent No. 4,863,952 discloses an improved method of drug administration using a mixture comprising pyrrolidone carboxylic acid esters as percutaneous promoters, and optionally, substituted ureas such as butylurea. S.K. Han et al. (1991, "Percutaneous Absorption-Enhancing Activity of Urea Derivatives," Arch. Pharm. Res. 14(1):12-18) disclose the use of urea derivatives, including butylurea, to enhance the percutaneous absorption of salicylic acid and sodium salicylate from a vaseline base.

Hydrogels are well known in the art as vehicles for the controlled release of drugs. N.A. Peppas, ed., "Hydrogels in Medicine and Pharmacy," CRC Press, Inc.

(1987) Vol. II, discloses the use of water soluble cellulose ethers such as methylcellulose for controlled release drug delivery systems. Volume III of the same publication discloses the release of progesterone from rod-shaped monolithic hydrogel devices.

U.S. Patent Nos. 5,344,655 and 5,254,338 disclose that hydrogel bases containing water soluble polymers such as cellulose derivatives are known in the art for delivery of drugs through the skin. U.S. Patent No. 4,693,887 discloses hydrogel compositions for the controlled release of contraceptives such as progesterone. The hydrogels are blends of either N-vinyl lactam or a copolymer of N-vinyl lactam and may further comprise spermicides such as urea. U.S. Patent No. 5,405,366 discloses an adhesive hydrogel comprising an aqueous mixture of a radiation crosslinkable water-soluble polymer such as a polymer of N-vinyl-2-pyrrolidone and ethylene oxide and a humectant such as propylene glycol which may be used in a transdermal drug delivery system. The hydrogel may also contain preservatives such as propyl paraben and methyl paraben. U.S. Patent No. 4,593,053 discloses a skin-compatible pressure-sensitive adhesive hydrogel comprising polyvinyl pyrrolidone and polyvinyl alcohol, a polar plasticizer or humectant such as propylene glycol, water and a drug. The composition may also contain cellulose derivatives to increase strength and guar gum to increase tackiness.

The transdermal delivery of progesterone, progestins, estrogens and testosterone from hydrogel matrices comprising permeation enhancers is also known. For example, U.S. Patent No. 5,030,629 discloses transdermal formulations containing progesterone, ethanol, saline and an imidazoline penetration enhancer. Dosage forms of the formulations for application to the skin include gels, which may comprise inert carriers such as propylene glycol, urea and methylcellulose. U.S. Patent No. 5,362,497 discloses compositions for transdermal delivery of, *inter alia*, androgens such as testosterone and estrogens such as estradiol comprising water- and fat-soluble absorption enhancers, and a water-absorbent resin such as a vinyl acetate-acrylic acid ester copolymer that swells to form a hydrogel upon contact with water. U.S. Patent No. 5,064,654 discloses a transdermal drug formulation comprising a drug such as progesterone or estradiol, water and ethanol. The formulation may also contain an

adhesive or gelling agent such as pectin, guar gum or methyl cellulose. U.S. Patent No. 4,942,158 discloses a composition comprising a combination of isopropyl alcohol and isobutyl alcohol to enhance the transdermal penetration of steroids such as estradiol, or a combination of estradiol with a progestogen. The composition may also include water and a gelling agent such as methyl cellulose. U.S. Patent No. 4,865,848 discloses compositions for enhancing the transdermal delivery of drugs, including progesterone, comprising sucrose esters as penetration enhancers. Preferably, the permeation enhancer and the drug are dispersed in a matrix which may be a gel or a hydrophilic polymer.

Despite their advantages, conventional transdermal delivery systems have been limited due to barrier properties of the stratum corneum, the skin's protective outer layer. Large, high molecular weight drugs such as progesterone are difficult to deliver through the skin in effective amounts. In general, the skin is highly resistant to permeation by chemicals, including drugs. Although the skin is only a few millimeters thick, the stratum corneum serves as a highly protective barrier against physical, chemical and bacterial penetration. This barrier primarily consists of dead skin cells bound together by certain fatty (lipid) materials. Generally, only drugs that are effective in the body at very low concentrations or that have particular physical properties have been successfully delivered through the skin in therapeutically effective amounts. High molecular weight drugs and drugs which are either charged or highly polar remain difficult to administer transdermally.

Natural progesterone, which is the form of progesterone that is produced by the body, has been administered in oral, injectable and suppository forms. The disadvantages of injectable and suppository forms are obvious: they are burdensome to administer. The disadvantage of oral forms is that they are short acting, and to maintain adequate blood levels, they have to be dosed throughout the day. The bulk of orally administered progesterone is metabolized by the digestive system and excreted before it can be used by the body. In fact, progesterone, whether administered orally, vaginally or rectally, has a half life in the body of only about 2.2 hours. Therefore, much larger amounts than the body actually requires must be dosed to maintain effective blood levels.

To address the problems associated with conventional means of administration of natural progesterone, a variety of synthetic forms, known as progestins, have been developed. Progestins fall primarily into two categories. The first group, pregnanes, is derived from 17-α-acetoxy progesterone. A classic example is medroxy progesterone acetate (Provera). With an increased affinity for progesterone receptors, these compounds have marked progestational activity. They possess anti-estrogenic anti-gonadotropic, and no significant androgenic properties. A second group, estranes, derived from 17-α-ethinyl-1-nortestosterone, includes norethindrone acetate (aygestin). Besides progestational activity, these compounds have marked anti-estrogenic, some anabolic, moderate androgenic, and as a result, pronounced anti-gonadotropic activities.

Synthetic progesterones are 10-100 times more potent than natural progesterone, and thus are effective at much lower doses. However, synthetic progesterones (i.e., progestins) can cause many negative side effects, such as sudden or partial loss of vision, thrombophlebitis, pulmonary embolism, cerebral thrombosis, salt and fluid retention, epilepsy, migraine, asthma, cardiac or renal dysfunction, weight gain, rise in blood pressure, headaches, depression, decreased glucose tolerance leading to diabetes in predisposed individuals, acne, alopecia, hirsutism, decrease in T3 uptake and thyroid regulation.

A disadvantage of conventional patch systems is that many of them either incorporate drugs in an adhesive or require an adhesive to affix the patch to patient's skin. These adhesives can irritate the skin, causing patient non-compliance. Thus, there is a need for a non-adhesive transdermal delivery system that can deliver therapeutically effective amounts of hormones such as natural progesterone, progestins, estrogens and testosterone that will reduce or eliminate the skin irritation experienced by many patients using current adhesive patch transdermal delivery systems. This need is satisfied by a particular embodiment of the invention.

Although patches for the transdermal delivery of estrogen and testosterone are currently commercially available, progesterone can be obtained commercially at present only in oral, injectable and suppository forms. The transdermal delivery of natural progesterone from hydrogel matrix systems with potential for use in patches has been demonstrated; however, none of these systems has proven adequate for administration of

therapeutically effective amounts of progesterone. Accordingly, there is a need in the art for a matrix composition that can transdermally deliver and maintain therapeutically effective levels of hormones such as natural progesterone, progestins, estrogens and testosterone in the bloodstream from a convenient, reliable patch system.

Citation of the references hereinabove shall not be construed as an admission that such references are prior art to the present invention.

## 3. SUMMARY OF THE INVENTION

The present invention is directed to compositions for the transdermal delivery of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a combination thereof, said compositions comprising or alternatively consisting or consisting essentially of: (a) a hydrogel, or a base mixture that when combined with water forms a hydrogel; (b) a permeation enhancer selected from the group consisting of urea, hydroxyurea, or an alkylurea; and (c) a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a combination thereof. In a preferred embodiment, the hormone is natural progesterone. Natural progesterone is superior to synthetic forms of progesterone, known as progestins, in treating gynecological conditions. The invention also provides apparatuses for transdermal hormone delivery containing the compositions of the invention. Methods of transdermal drug delivery, and of treatment of disorders responsive to the administration of hormones, are also provided.

Transdermal delivery according to the invention offers significant advantages over conventional means of drug administration. It is a comfortable, convenient and noninvasive means of drug delivery. The variable rates of absorption and metabolism encountered in oral treatment are avoided, and side effects such as gastrointestinal irritation and the like are eliminated. Transdermal drug delivery also makes possible a high degree of control over blood concentrations of particular drugs.

Transdermal drug delivery according to the invention also helps provide patients with a drug's maximum therapeutic effect and decreases the risk of adverse side effects or diminished therapeutic effect due to excessive or insufficient blood concentrations. The therapeutic effect of a drug is typically achieved only when the drug is within a

specific concentration range in the bloodstream. This blood concentration range is often called the drug's "therapeutic window." Below this range the drug may be ineffective, and above it the drug may cause unwanted side effects. Many conventional forms of drug delivery administer higher concentrations than are required in order to maintain effective blood levels between doses. However, blood levels often fall below effective concentrations prior to administration of the next dose. Transdermal drug delivery systems using the compositions of the present invention are designed to maintain a precise and continuous flow of drug into the bloodstream. This results in more stable blood concentrations which consistently remain within a drug's therapeutic window.

In contrast to oral administration, transdermal drug delivery can frequently maximize a drug's therapeutic effect by avoiding the gastrointestinal ("GI") tract and "first pass" liver metabolism. Oral drug delivery is often unreliable because the achievement of therapeutic blood levels depends on several factors, including the drug's chemical composition, the patient's physical condition, chemical and physical reactions between the drug and substances in the GI tract and the timing of drug administration. Upon GI tract absorption a drug must pass through the liver before entering the bloodstream. In many instances, the liver metabolizes a large portion of the drug. As a result, orally dosed drugs must generally be administered at levels which exceed optimal therapeutic levels, potentially resulting in adverse side effects.

Transdermal drug delivery systems according to the invention avoid many of the problems associated with conventional drug delivery, and are capable of conveniently and consistently delivering drugs over a number of hours or days. The transdermal drug delivery systems of the invention may also improve the safety of drug administration, since they can be removed quickly and easily. If a patient has an adverse reaction to a drug, rapid removal of the transdermal drug delivery device can minimize the extent of such an adverse reaction.

The present invention provides compositions comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride. The compositions of the present invention may further comprise a glycolic, alcoholic or oil-based additive such as propylene glycol. The compositions

may further comprise coloring, fragrance or other pharmaceutically acceptable additives. The compositions of the present invention may also comprise pectin.

In a preferred embodiment, compositions of the present invention consist essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben, sodium chloride and pectin.

Preferably, compositions of the present invention comprise 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin.

Even more preferably, the compositions comprise about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

In one embodiment, the compositions of the present invention further comprise a drug selected from the group consisting of nicotine, nitroglycerin, albuterol, VERAPAMIL®, scopolamine, n-butylurea, fentanyl, morphine, butaconazole, acetylsalicylic acid, MINOXIDIL®, lidocaine, racemic menthol, methyl salicylate, benzalkonium chloride, DEET®, phenobarbital, iodine, insulin, salicylic acid, nonoxynol-9, erythromycin, tetracycline, cephalosporins, and acetaminophen.

In a preferred embodiment, the compositions of the present invention further comprise a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl, or a lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl.

Preferably, the substituted urea is butylurea.

The compositions of the present invention may be provided in the form of a hydrogel comprising water and a base mixture, said base mixture comprising: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

The compositions of the present invention may be provided in the form of a dry powder comprising

(a) a drug; and

(b) a base mixture comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

The compositions of the present invention may also be provided in the form of a paste comprising

(a) a drug; and

(b) a base mixture comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

The present invention further provides compositions comprising:

(a) a hydrogel comprising water and a base mixture, said base mixture comprising or consisting essentially of: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride;

(b) a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl or a lower alkyl having from 1 to 8 carbon atoms; and

(c) a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing.

The compositions of the present invention may further comprise a glycolic, alcoholic or oil-based additive such as propylene glycol. The compositions may further comprise coloring, fragrance, or other pharmaceutically acceptable additives. The compositions of the present invention may also comprise pectin.

Preferably, the hydrogel-forming base mixture of the present invention consists essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben, pectin and sodium chloride.

More preferably, the hydrogel-forming base mixture of the present invention consists essentially of 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 0.75-3.5% pectin, and 1-3% sodium chloride. Even more preferably, the base mixture consists essentially of about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

Preferably, the compositions of the present invention consist essentially of:

(a) 3-12% of a base mixture as described above;

(b) 0.5-15% by weight of a substituted urea permeation enhancer of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms;

(c) 5-20% by weight of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, and a mixture of any two or more of the foregoing;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% water; in which said base mixture and water form a hydrogel.

Even more preferably, the compositions of the present invention consist essentially of:

(a) about 9% by weight of a base mixture consisting essentially of: about 63% (by weight) methyl cellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methylparaben, about 1.5% sodium chloride and about 3% pectin;

(b) about 2% by weight of a substituted urea of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms;

(c) about 10% by weight of progesterone;

(d) about 20% by weight propylene glycol; and

(e) about 59% by weight water; in which said base mixture and water form a hydrogel.

The compositions of the present invention may be used as vehicles or carriers for the delivery of a wide variety of drugs to a subject. Drugs that can be delivered using the compositions of the present invention include, but are not limited to nicotine, nitroglycerin, albuterol, VERAPAMIL®, scopolamine, n-butylurea, fentanyl, morphine, butaconazole, acetylsalicylic acid, MINOXIDIL®, lidocaine, racemic menthol, methyl salicylate, benzalkonium chloride, DEET®, phenobarbital, iodine, insulin, salicylic acid, nonoxynol-9, erythromycin, tetracycline, cephalosporins, and acetaminophen.

The compositions of the present invention are particularly useful as pharmaceutically acceptable bases for the delivery of drugs such as hormones selected from the group consisting of progesterone, progestin, estrogen, testosterone, and mixtures of any two or more of the foregoing. The compositions of the present invention are particularly useful for the transdermal delivery of these hormones. In a preferred embodiment, compositions of the present invention are particularly useful for the transdermal delivery of progesterone.

In another embodiment, the compositions of the present invention are useful in a variety of vaginal applications. For example, compositions of the present invention are useful as vaginal lubricants, spermicides, and to treat vaginal yeast infections.

In specific embodiments, the present invention provides devices for transdermal delivery of drugs that do not require the use of an adhesive that has the potential to irritate the skin.

Devices in accordance with the invention may comprise a watch, or are in the form of a watch. In one embodiment, a watch or watch-like device of the invention has a watch-case with a recessed chamber on the back face of the watch-case in contact with the skin. The recessed chamber contains a wafer having a top face and a bottom face containing a drug and a pharmaceutically acceptable base. In another embodiment, the recessed chamber of the watch-case comprises a fluid-filled or hydrogel cushion later situated against the top face of the drug-containing wafer. In another embodiment, the recessed chamber of the watch-case comprises a heating layer having a top face and a bottom face in which the bottom face of the heating layer is situated against the top face of the drug-containing wafer. In still another embodiment, the recessed chamber of the

watch-case comprises permanent, closed cell having a top face and a bottom face, the bottom face of which is situated against the top face of the heating layer.

In another embodiment, a device for the transdermal delivery of a drug to a subject is provided which comprises a disc-shaped drug reservoir. The reservoir has a recessed chamber which can contain a wafer having a top face and a bottom face comprising a drug and a pharmaceutically acceptable base. In one embodiment, the reservoir clips on to the back face of a watch or watch-like device such that drug-containing wafer is maintained in contact with the subject's skin. In another embodiment, the reservoir slides onto a band capable of being attached to the limb of a subject such that the drug-containing wafer is maintained in contact with the skin of the subject's limb. In another embodiment, the recessed chamber of the clip-on or slide-on drug reservoir comprises a fluid-filled or hydrogel cushion later situated against the top face of the drug-containing wafer. In another embodiment, the recessed chamber of the clip-on or slide-on drug reservoir comprises a heating layer having a top face and a bottom face in which the bottom face of the heating layer is situated against the top face of the drug-containing wafer. In still another embodiment, the recessed chamber of the clip-on or slide-on drug reservoir comprises permanent, closed cell having a top face and a bottom face, the bottom face of which is situated against the top face of the heating layer.

In another embodiment, a device for the transdermal delivery of a drug to a subject in accordance with the present invention comprises a glove wherein the inside of the glove is lined with a layer containing a composition of the invention comprising a pharmaceutically acceptable hydrogel base and a drug.

In still another embodiment, a device for the transdermal delivery of a drug to a subject in accordance with the present invention comprises a band or a strap having a surface coated with a drug-containing composition of the present invention, wherein the band or strap is capable of being attached to the limb of a subject such that the drug-containing composition is maintained in contact with the skin of the subject's limb.

The present invention also provides kits comprising the recessed chamber-type, the clip-on drug reservoir-type, the slide-on drug reservoir-type, the glove-type or the band-type of transdermal drug delivery devices.

The present invention als provides methods for the treatment of conditions responsive to hormone replacement therapy such as premenstrual syndrome, menopause, infertility, dysfunctional bleeding, corpus luteum failure, senile vulvo-vaginitis, hypogonadism and osteoporosis. The invention also provides methods of contraception in males and females. The invention further provides a method of delivering a hormone or mixture of hormones to a subject. These methods of the invention involve placing a composition of the invention in contact with the skin of a subject such that an effective amount of the hormone or mixture of hormones is delivered transdermally to said subject.

The present invention also provides methods for the treatment of vaginal disorders such as yeast infections. The present invention also provides methods of providing contraception using spermicides. The present invention further provides methods for providing vaginal lubrication. These methods involve placing a composition of the present invention inside the vagina of a subject.

## 4. DESCRIPTION OF THE FIGURES

Figure 1. Cross-sectional view of a Membrane-Moderated Transdermal Drug Delivery System. The system comprises: a drug reservoir 1 that may contain a composition of the present invention; a drug-impermeable backing layer 2, which can be plastic, metal, metallic laminate or any other pharmaceutically acceptable material; a rate-controlling polymeric membrane 3; and an adhesive layer 4, which can be any adhesive known in the art. Arrows 5 show an exemplary route of passage of the drug out the device into the skin. Figure 1 is adapted from R. Sitruk-Ware, 1989, "Transdermal Delivery of Steroids," Contraception 39 (1):1-20, at page 9, Figure 5.

Figure 2. Cross-sectional view of an Adhesive Diffusion-Controlled Transdermal Drug Delivery System. The system comprises: a drug reservoir layer 1 which may comprise a composition of the present invention; a drug-impermeable backing layer 2, which can be plastic, metal, metallic laminate or any other pharmaceutically acceptable material; a rate-controlling adhesive layer 3; and an adhesive layer 4. The adhesive layers may comprise any adhesive known in the art. Arrows 5 show an exemplary route of passage of the drug out the device into the skin. Figure 2 is adapted from R.

Sitruk-Ware, 1989, "Transdermal Delivery of Steroids," Contraception 39 (1):1-20, at page 10, Figure 6.

Figure 3. Cross-sectional view of a Microreservoir-Type Transdermal Drug Delivery System. The system comprises: an adhesive foam pad 1 made of flexible polyurethane; an occlusive baseplate 2 comprising an aluminum foil disc; an adhesive rim 3; microscopic drug reservoirs 4; and a polymer matrix 5 which may comprise a composition of the present invention. Arrows 6 show an exemplary route of passage of the drug out the device into the skin. Figure 3 is adapted from R. Sitruk-Ware, 1989, "Transdermal Delivery of Steroids," Contraception 39 (1):1-20, at page 12, Figure 8.

Figure 4. Cross-sectional view of a Matrix Dispersion-Type Transdermal Drug Delivery System. The system comprises: a drug-impermeable backing layer 1, which may be plastic, metal, metallic laminate or any other pharmaceutically acceptable material; an absorbent pad 2; an occlusive baseplate 3 comprising an aluminum foil disc; a drug reservoir 4 which may contain a composition of the present invention; and an adhesive rim 5. Arrows 6 depict an exemplary route of passage of the drug out the device into the skin. Figure 4 is adapted from R. Sitruk-Ware, 1989, "Transdermal Delivery of Steroids," Contraception 39 (1):1-20, at page 11, Figure 7.

Figure 5. Perspective view of the top face of a recessed-chamber type of transdermal drug delivery device of the present invention, comprising: a watch case 1 and a band or strap 2.

Figure 6. Perspective view of the back face of one embodiment of the recessed-chamber type of transdermal drug delivery device of the present invention, comprising: a watch case 1; a recessed chamber 2 capable of containing a wafer comprising a drug and a pharmaceutically acceptable base, which may comprise a composition of the present invention; and a band or strap 3.

Figure 7. Cross-sectional view of one embodiment of the recessed-chamber type of transdermal drug delivery device of the present invention, comprising: a watch case 1; a recessed chamber 2; a band or strap 3; and a wafer 4 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention.

Figure 8. Cross-sectional view of another embodiment of the recessed-chamber type of transdermal drug delivery device of the present invention, comprising: a watch case 1; a recessed chamber 2; a band or strap 3; a fluid-filled cushion 4; a wafer 5 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention; and a non-slip material 6 on the rim of the recessed chamber.

Figure 9. Perspective view of one embodiment of the top face of a watch or watch-like device having the clip-on drug reservoir type of transdermal drug delivery device of the present invention attached to its back face comprising: a watch case 1; a band or strap 2; and a clip-on drug reservoir 3.

Figure 10. Cross-sectional view of one embodiment of the clip-on or slide-on drug reservoir type of transdermal drug delivery device of the present invention, comprising: a plurality of clips 1 capable of attaching the clip-on drug reservoir to the back face of a watch or watch-like device; a recessed chamber 2; a wafer 3 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention; and a soft flair skin seal 4.

Figure 11. Cross-sectional view of another embodiment of the clip-on or slide-on drug reservoir type of transdermal drug delivery device of the present invention, comprising: a plurality of clips 1 capable of attaching the drug reservoir to the back face of a watch or watch-like device; a recessed chamber 2; a permanent closed cell 3 comprising dense polyethylene capable of providing slight downward pressure on the drug-containing wafer; a heating layer 4 comprising a means for heating the drug-containing wafer; a wafer 5 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention; and a soft flair skin seal 6.

Figure 12. Perspective view of the bottom face of one embodiment of the clip-on or slide-on drug reservoir type of transdermal drug delivery device of the present invention, comprising: a plurality of clips 1 capable of attaching the clip-on drug reservoir to the back face of a watch or watch-like device; a recessed chamber 2; a soft flair skin seal 3; and a plurality of slots 4 that are capable of having a band or strap threaded through them.

Figure 13. Cross-sectional view of a watch having one embodiment of the clip-on drug reservoir type of transdermal drug delivery device of the present invention attached to its back face, comprising: a watch case 1; a band or strap 2; a clip-on drug reservoir 3; a recessed chamber 4; a wafer 5 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention; and a soft flair skin seal 6.

Figure 14. Cross-sectional view of one embodiment of the slide-on drug reservoir type of transdermal drug delivery device of the present invention attached to a band, comprising: a slide-on drug reservoir 1; a band or strap 2; a recessed chamber 3; a wafer 4 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention; and a soft flair skin seal 5.

Figure 15. Perspective view of the bottom face of one embodiment of the slide-on drug reservoir type of transdermal drug delivery device of the present invention, comprising: a plurality of slots 1 that are capable of having a band or strap threaded through them; a wafer 2 comprising a drug and a pharmaceutically acceptable base which may comprise a composition of the present invention; a soft flair skin seal 3; and a band or strap 4.

Figure 16. Cross-sectional view of the Single-Chamber Diffusion Cell used in the skin permeation measurements described in Section 6.2. The cell comprises: a retaining nut 1; a flanged PVC washer 2 with aluminum foil coating 3; an o-ring 4; a skin disc 5, which is cemented to a nylon washer 6; a teflon-coated magnetic stirring button 7; receptor fluid 8; and a stopper 9 comprising a foil-coated flanged washer.

Figure 17. A graph depicting the cumulative amount of progesterone penetrated, ($\mu g/cm^2$, y-axis) against time, (hours x-axis), from sample A-1 through a dialysis membrane, as described in Section 6.2.2. The graph shows a penetration rate of 30.8 $\mu g/cm^2$ of progesterone through the dialysis membrane.

Figure 18. A graph depicting the cumulative amount of progesterone penetrated, ($\mu g/cm^2$, y-axis) against time, (hours, x-axis), from covered and not-covered samples of A-1 through human skin, as described in Section 6.2.3. Curve 1 corresponds to the covered sample of A-1 and Curve 2 corresponds to the not-covered sample of A-1.

Figure 19. A graph depicting the cumulative amount of progesterone penetrated, ($\mu g/cm^2$, y-axis) against time, (hours, x-axis), from samples A-1, A-2, and A-3 through human skin, as described in Section 6.2.4. Curve 1, corresponding to sample A-1, shows a rate of 3.1 $\mu g/cm^2/hr$. Curve 2, corresponding to sample A-2, shows a rate of 1.9 $\mu g/cm^2/hr$. Curve 3, corresponding to sample A-3, shows a rate of 9.8 $\mu g/cm^2/hr$.

Figure 20. Cross-sectional view of the redesigned Diffusion Cell Assembly used in the skin permeation measurements described in Section 6.4. The cell comprises: a glass receptor 1; a magnetic stirrer 2; saline 3; a teflon washer 4; a notch which eliminates air bubbles 5; an assembled donor 6; a donor chamber 7; test material on epidermal membrane cemented to nylon washer 8; a foil cover 9; an O-ring 10; a flanged washer 11; and a nut 12.

Figure 21. Progesterone penetration of human skin *in vitro*. A graph depicting the cumulative amount of progesterone penetrated ($\mu g/cm^2$, y-axis) against time (hours, x-axis) from samples A-4 (curve 2) and B-4 (curve 1), as described in Section 6.4. The graph shows a mean penetration rate (m) of 6.1 $\mu g/cm^2/hr$ for sample A-4 ($R^2$ = 0.9989) and a mean penetration rate (m) of 3.2 $\mu g/cm^2/hr$ for sample B-4 ($R^2$ = 0.9984).

## 5. DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

The compositions of the present invention may further comprise a glycolic, alcoholic or oil-based additive. Examples of the glycolic, alcoholic, or oil-based additives that may be used in the compositions of the present invention include, but are not limited to propylene glycol, glycerin, mineral oil, corn oil, bran oil, rice oil, soy oil, ethylene glycol, xylene and alcohols such as ethyl alcohol. A preferred additive is propylene glycol. The compositions may further comprise coloring, fragrance or other pharmaceutically acceptable additives. The compositions of the present invention may also comprise pectin.

In a preferred embodiment, compositions of the present invention consist essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben, sodium chloride and pectin.

Preferably, compositions of the present invention comprise 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin. Even more preferably, the compositions comprise about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

In specific embodiments, drugs are included in the compositions of the present invention.

In a preferred embodiment, the compositions of the present invention further comprise a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl, or a lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl. Preferably, the substituted urea is butylurea.

The compositions of the present invention may be provided in the form of a dry powder comprising

(a) a drug; and

(b) a base mixture comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

The compositions of the present invention may also be provided in the form of a paste comprising

(a) a drug; and

(b) a base mixture comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

Dry powder and paste compositions of the present invention can form hydrogels upon the addition of water.

The present invention provides compositions for the transdermal delivery or hormones such as progesterone, progestin, estrogen, testosterone, or combinations thereof, said compositions alternatively consisting of or consisting essentially of: (a) a hydrogel, or a base mixture that when combined with water forms a hydrogel; (b) a permeation enhancer selected from the group consisting of urea, hydroxyurea, or an alkylurea; and (c) a hormone selected from the group consisting of progesterone, progestin, estrogen, testosterone, or combinations thereof. In preferred embodiment, the hormone is natural progesterone. Natural progesterone is superior to synthetic forms of progesterone, known as progestins, in treating gynecological conditions.

The invention also provides apparatuses for transdermal hormone delivery containing the compositions of the invention. Methods of transdermal delivery, and of treatment of disorders responsive to the administration of hormones are also provided. The compositions of the invention provide more effective and efficient means for delivery of a therapeutically effective amount of the hormone(s) contained therein to the bloodstream of a patient.

The present invention further provides compositions comprising:

(a) a hydrogel comprising water and a base mixture, said base mixture comprising or consisting essentially of: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride;

(b) a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl or a lower alkyl having from 1 to 8 carbon atoms; and

(c) a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing.

The composition may also optionally contain a glycolic, alcoholic or oil-based additive. Examples of the glycolic, alcoholic or oil-based additives that may be used in the compositions of the present invention include propylene glycol, glycerin, mineral

oil, corn oil, bran oil, rice oil, soy oil, ethylene glycol, xylene, and alcohols such as ethyl alcohol. A preferred additive is propylene glycol. The compositions may also contain colorings, fragrances or other pharmaceutically acceptable additives. Preferably, the water used in the inventive compositions is distilled water. The compositions of the present invention may also comprise pectin.

Preferably, the hydrogel-forming base mixture of the present invention consists essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben, pectin and sodium chloride.

More preferably, the hydrogel-forming base mixture of the present invention consists essentially of 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 0.75-3.5% pectin, and 1-3% sodium chloride. Even more preferably, the base mixture consists essentially of about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

Preferably, the compositions of the present invention consist essentially of:

(a) 3-12% of a base mixture as described above;

(b) 0.5-15% by weight of a substituted urea permeation enhancer of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms;

(c) 5-20% by weight of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, and a mixture of any two or more of the foregoing;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% water; in which said base mixture and water form a hydrogel.

Even more preferably, the compositions of the present invention consist essentially of:

(a) about 9% by weight of a base mixture consisting essentially of: about 63% (by weight) methyl cellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methylparaben, about 1.5% sodium chloride and about 3% pectin;

(b) about 2% by weight of a substituted urea of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms;

(c) about 10% by weight of progesterone;

(d) about 20% by weight propylene glycol; and

(e) about 59% by weight water; in which said base mixture and water form a hydrogel.

## 5.1 HYDROGEL BASE MIXTURE

The hydrogel-forming base mixture may optionally include pectin.

Natural gums which may be used in the hydrogel-forming base mixture include guar gum and xanthin gum. The hydrogel-forming base mixture preferably comprises a methylcellulose gelling agent; however inclusion of methylcellulose is not required. In place of the methylcellulose gelling agent, additional amounts of natural gums such as guar or xanthin gums, or mixtures thereof, may be substituted.

The hydrogel-forming base mixture of the present invention is preferably made by way of example as follows: A dry powder form is mixed together of each of the natural gum, glucose, propylparaben, methylparaben, and sodium chloride ingredients. Methyl cellulose and pectin dry powders are optionally included. The dry powder mixture is then micronized to a size of approximately one micron. Upon the addition of water, the mixture forms a hydrogel, which varies from a semi-fluid to a solid rubber consistency, depending on the amount of water added.

Preferably, the hydrogel-forming base mixture of the present invention consists essentially of 50-80% (percentages are by weight) methyl cellulose, 15-25% of a natural gum, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, and 1-3% sodium chloride. Optionally, the mixture may include 0.75-3.5% pectin. Even more preferably, the base mixture consists essentially of 63% methylcellulose, 21% guar gum, 5% glucose, 3.5% propylparaben, 3% methyl paraben, 3% pectin and 1.5% sodium chloride. All seven of these ingredients that may be used in the base mixture of the present invention are well known materials which are readily available from a wide

variety of commercial sources such as the Aldrich Chemical Co. (Milwaukee, WI), or the Sigma Chemical Co. (St. Louis, MO), etc.

In preferred embodiment, the present invention provides a composition for the transdermal delivery of natural progesterone comprising, or alternatively, consisting essentially of:

(a) 3-12% of a base mixture comprising: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or mixtures thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride; which may optionally include pectin;

(b) 0.5-15% by weight of a substituted urea permeation enhancer of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms;

(c) 5-20% by weight of a hormone selected from the group consisting of progesterone, progestins, estrogens, and testosterone, or mixtures thereof;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% water; in which said base mixture and water combine to form a hydrogel.

A particularly preferred embodiment of the present invention is directed to a composition for the transdermal delivery of natural progesterone consisting of:

(a) 9% by weight of a base mixture consisting essentially of (1) methylcellulose; (2) guar gum; (3) glucose; (4) propylparaben; (5) methyl paraben; (6) pectin; and (7) sodium chloride;

(b) 2% by weight of a substituted urea permeation enhancer of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms;

(c) 10% by weight of natural progesterone;

(d) 20% by weight propylene glycol; and

(e) 59% by weight water; in which said base mixture and water form a hydrogel.

In a preferred embodiment, the above composition of the present invention is formed by first mixing the base mixture powder, substituted alkyl urea and progesterone

in propylene glycol to form a paste. The paste is then heated without boiling until the progesterone and substituted alkyl urea are dissolved and the paste becomes a liquid. This hot glycol mixture is then added to tepid water while stirring with a blade type stirring unit at a speed sufficient to from a vortex at the surface. The hot glycol mixture is added to the stirring water in this manner for 5 to 15 minutes, or until the proper or desired viscosity is achieved. The mixture is then removed from the stirred container and placed in a barrier container for storage to prevent evaporation. Shelf life of the finished product should be several years.

## 5.2 PERMEATION ENHANCERS

The compositions enhancers of the present invention can comprise monosubstituted lower-alkyl ureas of the formula:

$$R\text{-}NH\text{-}CO\text{-}NH_2$$

wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms. Preferably, the lower alkyl group has from 1 to 6 carbon atoms; more preferably from 1 to 4 carbon atoms; and most preferably from 3 to 4 carbon atoms. Specific examples of the lower alkyl group R include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl. A particularly preferred monosubstituted lower-alkyl urea useful in the present invention is butylurea. The monosubstituted lower alkyl ureas are known compounds and are readily available from commercial sources such as the Aldrich Chemical Co. (Milwaukee, WI). In a preferred embodiment, the permeation enhancer is butylurea. When the compositions of the present invention comprising urea derivatives are used for the transdermal delivery of drugs, the urea derivatives may function as transdermal penetration enhancers. Urea derivatives such as butylurea can also function as spermicides when the compositions of the present invention are used in vaginal applications.

## 5.3 DRUGS

Drugs which may be used in the compositions of the present invention and the disorders which such compositions may be used to treat include, but are not limited to nicotine for smoking cessation, nitroglycerin for angina pectoris, albuterol as an

antiasthmatic, VERAPAMIL for hypertension, scopolamine for motion sickness, n-butylurea for herpes sores, fentanyl for acute pain, morphine for pain, steroid hormones for osteoporosis, estrogen and progestin for hormonal replacement, butaconazole for vaginal yeast infection, acetylsalicylic acid as aspirin for pain, MINOXIDIL® for hair growth, lidocaine for pain, racemic menthol for pain, methyl salicylate for pain, benzalkonium chloride as a germicide, DEET® for insect control, phenobarbital as a sedative, iodine as an antiseptic, insulin as an antidiabetic, salicylic acid as a topical keratolytic, nonoxynol-9 as a spermicide, erythromycin as an antibiotic, tetracycline as an antibiotic, cephalosporins as an antibiotic, and acetaminophen for pain. In a specific embodiment, the drug has utility in the treatment of a human disease or animal disorder. The present invention also provides methods for treating the above-listed disorders.

Examples of hormones that may be delivered to a subject using the compositions of the present invention include progesterone, progestin, estrogen and testosterone, or a mixture of any two or more of the foregoing. Depending on the application, the present invention may be used to deliver each of these hormones alone, or in various combinations. In a preferred embodiment, the hormones are delivered transdermally using the compositions of the present invention. Specific examples of progestins useful in the present invention include but are not limited to are medroxy progesterone acetate, norethindrone, norethindrone acetate, norgestrel, and ethynodiol diacetate. Specific examples of estrogens useful in the present invention include but are not limited to 17-$\beta$-estradiol, diethylstilbestrol, estropipate (formerly known as piperazine estrone sulfate), estrone and estriol.

A most preferred hormone is pregn-4-ene-3,20-dione, which has a molecular weight of 314.47, and is also known as "natural progesterone", or simply, "progesterone." Natural progesterone is produced in the human body, but it can be also be isolated from certain plants, and is available commercially. For example, micronized powder forms of natural progesterone useful in the present invention are available from both the Upjohn Chemical Co. (Kalamazoo, MI) and the Berlex Chemical Co. (North Surburban, IL).

As discussed above, the compositions of the present invention are also suitable for delivery, transdermal and otherwise, of synthetic progestins, estrogens such as 17-β-estradiol and testosterone. Synthetic progestins, estrogens and testosterone which may be used in the present invention are readily available from a variety of commercial sources well known to those skilled in the art.

## 5.4 TRANSDERMAL DELIVERY DEVICES

The means for administration of the compositions of the present invention to a patient may vary. In one embodiment, compositions of the present invention are administered vaginally. In another embodiment, the compositions are delivered transdermally, which but necessarily involves application of the composition to a selected intact surface of the skin for a period of time sufficient to provide the desired blood level of the drug. Preferably, the composition is administered to a patient via use of a transdermal delivery device. Various transdermal systems are known and may be used to administer therapeutically effective amounts of hormones using the compositions of the invention. Four general types of transdermal drug delivery devices are taught, for example, by R. Sitruk-Ware (1989, "Transdermal Delivery of Steroids," Contraception 39 (1):1-20. Transdermal delivery devices are also disclosed by Pfister and Hsieh (1990, "Permeation Enhancers Compatible with Transdermal Drug Delivery Systems: Part II: System Design Considerations," Pharmaceutical Technology (October 1990): 55-60.

For example, the composition of the present invention may be administered using a membrane-moderated transdermal drug delivery system, as shown in Figure 1. In this type of system, the inventive composition is contained within the drug reservoir 1. The rate of delivery of the hormone through the skin is simultaneously enhanced by use of the hydrogel and the monosubstituted alkyl urea penetration enhancer of the invention and moderated by a rate-controlling polymeric membrane 3. The inventive composition may also be administered to a patient via an adhesive diffusion-controlled transdermal drug delivery system, (see Figure 2) in which the rate of delivery of the hormone through the skin is simultaneously enhanced by use of the hydrogel and the

monosubstituted alkyl urea penetration enhancer of the invention and moderated by a rate-controlling adhesive layer 3.

Another type of transdermal drug delivery device suitable for use with the present invention is the microreservoir-type system (see Figure 3). As applied to the present invention, this type of system consists of a suspension of the solid hormone in the inventive hydrogel-forming base mixture. The hormone suspension is dispersed homogeneously in a lipophilic polymer to form numerous microscopic spheres of drug reservoir 4. This dispersion is thermodynamically unstable and is stabilized by cross-linking the polymer chains in situ. The mixture is formed into a disc and is then covered by an occlusive baseplate 2 and optionally surrounded by an adhesive rim 3.

A preferred transdermal delivery device useful for application of the compositions of the present invention is a matrix dispersion type system (Figure 4). For use in this type of system, the composition of the present invention is molded into a disc of a certain thickness and is applied onto an occlusive baseplate 3 in a compartment fabricated from a drug-impermeable plastic backing 1. An adhesive may be applied along the circumference of the device to form an adhesive rim 5 around the disc.

Generally, adhesives used in transdermal delivery devices have the potential to cause skin irritation. Accordingly, in specific embodiments, the present invention provides transdermal delivery devices in form of a watch or watch-like device which have the advantage that an adhesive is not necessary to maintain contact of a drug-containing transdermal delivery composition with the patient's skin.

In one embodiment, a watch or watch-like device of the invention has a watch-case with a recessed chamber on the back face of the watch-case in contact with the skin. The recessed chamber contains a wafer having a top face and a bottom face containing a drug and a pharmaceutically acceptable base. In another embodiment, the recessed chamber of the watch-case comprises a fluid-filled or hydrogel cushion later situated against the top face of the drug-containing wafer. In another embodiment, the recessed chamber of the watch-case comprises a heating layer having a top face and a bottom face in which the bottom face of the heating layer is situated against the top face of the drug-containing wafer. In still another embodiment, the recessed chamber of the

watch-case comprises permanent, closed cell having a top face and a bottom face, the bottom face of which is situated against the top face of the heating layer.

The heating layer of the inventive devices can comprise a printed circuit board or a plastic or metallic layer which contains a plurality of metal electrical wires or lines comprising circuitry which provide heating. The heating layer of the inventive devices can be battery-powered or solar-powered. In one embodiment the heating layer is powered via the battery of the watch. In another embodiment, the heating layer is powered by a solar cell.

The permanent, closed cell layer of the inventive devices can comprise a dense polymeric material. The permanent closed cell layer provides sight downward pressure on the drug filled wafer, to aid in maintaining contact of the wafer with the subject's skin.

In another embodiment, a device for the transdermal delivery of a drug to a subject is provided which comprises a disc-shaped drug reservoir. The reservoir has a recessed chamber which can contain a wafer having a top face and a bottom face comprising a drug and a pharmaceutically acceptable base. The drug reservoir may comprise clear plastic or vinyl.

In one embodiment, the reservoir clips on to the back face of a watch or watch-like device such that drug-containing wafer is maintained in contact with the subject's skin. In a specific embodiment, the reservoir clips over the posts and band of the wafer. In another embodiment, the reservoir slides onto a band capable of being attached to the limb of a subject such that the drug-containing wafer is maintained in contact with the skin of the subject's limb. In another embodiment, the recessed chamber of the clip-on or slide-on drug reservoir comprises a fluid-filled or hydrogel cushion later situated against the top face of the drug-containing wafer. In another embodiment, the recessed chamber of the clip-on or slide-on drug reservoir comprises a heating layer as described above having a top face and a bottom face in which the bottom face of the heating layer is situated against the top face of the drug-containing wafer. In still another embodiment, the recessed chamber of the clip-on or slide-on drug reservoir comprises permanent, closed cell as described above having a top face

and a bottom face, the bottom face of which is situated against the top face of the heating layer.

In another embodiment, a device for the transdermal delivery of a drug to a subject in accordance with the present invention comprises a glove wherein the inside of the glove is lined with a layer containing a composition of the invention comprising a pharmaceutically acceptable hydrogel base and a drug.

In still another embodiment, a device for the transdermal delivery of a drug to a subject in accordance with the present invention comprises a band or a strap having a surface coated with a drug-containing composition of the present invention, wherein the band or strap is capable of being attached to the limb of a subject such that the drug-containing composition is maintained in contact with the skin of the subject's limb.

The present invention also provides kits comprising the recessed chamber-type, the clip-on drug reservoir-type, the slide-on drug reservoir-type, the glove-type or the band-type of transdermal drug delivery devices.

In the case of the recessed-chamber water type of transdermal drug delivery device, the kit may comprise a watch or watch-like device with a recessed chamber and comprising a band or strap, and a plurality of drug-containing wafers. The wafers may be provided in sealed packages for long shelf life. In the case of the clip-on or slide-on type of transdermal drug delivery device, the kit may comprise at least one drug reservoir, which may be clear plastic, vinyl or some other acceptable material, and a plurality of drug-containing wafers. Again, the wafers may be provided in sealed packages for long shelf life.

One embodiment of the watch-like device of the present invention provides a recessed-chamber type of transdermal drug delivery device. A perspective view of the front face of this device is shown in Figure 5. The device comprises a watch case (1) and a band or strap (2) to attach the device to a limb (e.g., wrist, arm or leg) of the user. The back face (Figure 6) of the device has a recessed-chamber capable (2) of containing a drug-containing wafer, which may comprise a composition of the present invention. In a specific embodiment, the recessed chamber of the watch is approximately 3.6 cm in diameter, corresponding to an area of about 10 $cm^2$. The chamber is at least deep enough to accommodate a drug-containing wafer approximately

1.5 mm thick. When the wafer loses its ability to deliver the drug, the patient can simply replace it with another "refill" wafer.

The watch case may comprise stainless steel or plastic, and the recessed chamber may be lined with teflon or some other inert material. Optionally, the rim of the recessed chamber is coated with a non-slip or a soft flair skin seal material to aid in maintaining contact of the drug-containing wafer with the user's skin, and to prevent the drug-containing wafer from drying out. The front face of the watch need not actually contain a functional watch dial, although such can be the case.

Another embodiment of the recessed-chamber type of transdermal drug delivery device, shown in Figure 8, comprises a recessed chamber 2 deep enough to contain both a drug-containing wafer 2 and a fluid-filled cushion 4. The fluid-filled cushion may comprise the hydrogel alone, without the hormone. In a specific embodiment, the recessed chamber is deep enough to accommodate both a 1.5 mm thick hormone-containing wafer and a fluid-filled cushion on the roof of the chamber. This fluid cushion prevents the wafer from buckling and minimizes air bubbles. The device of this embodiment may also comprise a soft, non-slip material 6 on the rim of the recessed chamber.

Another embodiment of the watch-like device of the present invention provides a clip-on drug reservoir type of transdermal drug delivery device. A perspective view of the top face of the clip-on drug reservoir type transdermal drug delivery device of the present invention is shown in Figure 9, comprising a watch case 1, a band or strap 2 and a clip-on drug reservoir 3. The clip-on drug reservoir transdermal drug delivery device of the present invention (Figure 10) comprises a plurality of clips 1 capable of attaching the clip-on drug reservoir to the back face of a watch; a recessed chamber 2; a drug-containing wafer 3 which may comprise a composition of the present invention; and a soft flair skin seal 4. The front face of the watch need not actually contain a functional watch dial, although such can be the case.

Figure 13 shows a cross-sectional view of a watch having the clip-on drug reservoir type of transdermal drug delivery device of the present invention attached to its back face, comprising: a watch case 1; a band or strap 2; the clip-on drug reservoir

3 of the present invention; a recessed chamber 4, a drug-containing wafer 5; and a soft flair skin seal 6.

Another preferred embodiment of the present invention which also eliminates the need for an adhesive is a glove lined with the hormone-containing composition of the present invention. The glove may be latex or any material that is compatible with the compositions of the present invention. This embodiment of the invention is suitable when 24 hour contact of patient's skin with the hormone-containing composition of the invention is not necessary to achieve therapeutically effective blood levels of the hormone. The patient simply wears the lined gloves to bed and then removes them in the morning and washes their hands.

In another preferred embodiment of the invention, a means is provided for heating the hormone-containing composition while it is in contact with the patient's skin. Such heating increases the rate of penetration of the drug into the patient's bloodstream. For example, a battery-powered heater capable of warming the system approximately 10° F above ambient temperature can be built into the watch-like transdermal device of the present invention to increase the delivery rate of the hormone through the patient's skin.

In preferred embodiments, use of the compositions of the invention does not involve topical pre-administration of acetone or similar solvents in order to achieve transdermal delivery of therapeutically effective amounts to the bloodstream.

### 5.5 THERAPEUTIC USES

As discussed above, the compositions of the present invention may contain a wide variety of drugs, and may be used to treat a wide variety of disorders. In a preferred embodiments, the present invention provides methods for treatment of disorders responsive to the administration of hormones comprising administering to the patient transdermally a composition of the invention comprising a therapeutically effective amount of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, and a mixture of any two or more of the foregoing.

The compositions of the present invention are useful for treating a variety of disorders which benefit from hormone replacement therapy, including premenstrual syndrome, menopausal symptoms, infertility, and osteoporosis. A variety of gynecological problems in women such as dysfunctional bleeding, corpus luteum failure, and post-menopausal senile vulvo-vaginitis may also be treated with the compositions of the present invention, as well as male disorders such as hypogonadism. The compositions of the present invention may also be used to provide contraception to male and female subjects.

The subject is preferably an animal, including but not limited to animals such as cows, pigs, chickens, etc., and is preferably a mammal, and most preferably human. Human subjects may be male or female. Obviously, when the condition being treated is one specific to women, such as premenstrual syndrome, menopausal symptoms, and gynecological problems, the subject is a woman.

The present invention provides compositions useful for providing contraception to female subjects comprising progesterone, progestins, estrogens and mixtures thereof. Specifically, compositions of the present invention comprising progesterone, mixtures of progesterone and one or more estrogens, or mixtures of one or more estrogens and one or more progestins may be used to provide contraception to females. Compositions of the present invention comprising testosterone are useful for providing contraception to male subjects.

Compositions of the present invention comprising estrogen are particularly useful in treatment of menopause. At the onset of menopause, women lose their ability to produce estrogen. A diminished estrogen supply in post-menopausal women can cause such symptoms as hot flashes, insomnia, vaginal atrophy, irritability, anxiety, moodiness and excessive sweating. Natural or synthetic estrogens may be formulated into the compositions of the present invention for the treatment of these menopausal symptoms. Estrogen alone may be used to treat menopause in some women. However, women who use estrogen and who have an intact uterus preferably also take progesterone to prevent uterine cancer.

Compositions of the present invention comprising estrogen, progesterone or mixtures thereof may be used to treat or prevent osteoporosis. Estrogen is known to

prevent bone loss, while progesterone is known to stimulate bone growth. Osteoporosis is a progressive deterioration of the skeletal system through the loss of bone mass, and is related to the inability to produce estrogen. According to the National Osteoporosis Foundation, osteoporosis currently affects approximately 25 million people in the United States. It is estimated that 80% of all hip fractures in elderly patients are associated with osteoporosis.

Corpus luteum failure is another condition that the compositions of the present invention may be used to treat, and can result in infertility and/or irregular bleeding.

Compositions of the present invention comprising low dosages of testosterone can be used to treat senile vulvo-vaginitis, a post-menopausal condition.

Compositions of the present invention comprising natural progesterone, synthetic progestins, estrogens and mixtures thereof may be used to provide contraception to a subject.

Accordingly, the present invention provides methods for the treatment of premenstrual syndrome, menopausal symptoms, infertility, osteoporosis, dysfunctional bleeding, corpus luteum failure, post-menopausal senile vulvo-vaginitis and hypogonadism, and methods for providing contraception, by using compositions of the present invention containing one or more hormones. The methods entail providing a composition of the present invention comprising a hydrogel-forming base mixture, a skin permeation enhancer, a hormone selected from the group consisting of natural progesterone, progestins, estrogens, testosterone and mixtures thereof, an optional glycolic, alcoholic or oil-based additive, and water, and contacting said composition to the skin of a patient to permit the hormone in the composition to be absorbed into the skin.

In one embodiment, the present invention provides a method for the treatment of premenstrual syndrome in which a composition of the present invention comprising natural progesterone is contacted with the skin of a patient suffering from premenstrual syndrome. In another embodiment, the present invention provides a method for the treatment of menopausal symptoms such as hot flashes, insomnia, vaginal atrophy, irritability, anxiety, moodiness and excessive sweating in which a composition of the present invention comprising a hormone selected from the group consisting of natural

progesterone, progestins, estrogens, testosterone, and mixtures thereof, is contacted with the skin of a patient suffering from any of such symptoms. In another embodiment, the present invention provides a method for the treatment of infertility in which a composition of the present invention comprising natural progesterone is contacted with the skin of a patient suffering from any of such symptoms.

In still another embodiment, the present invention provides a method for the treatment of osteoporosis in which a composition of the present invention comprising natural progesterone, estrogen, or a mixture thereof is contacted with the skin of a patient suffering from osteoporosis. In still another embodiment, the present invention provides a method for the prevention of osteoporosis in which a composition of the present invention comprising natural progesterone, estrogen, or a mixture thereof is contacted with the skin of a patient who has the potential to develop osteoporosis.

In another embodiment, the present invention provides a method for the treatment of dysfunctional bleeding in which a composition of the present invention comprising natural progesterone or a mixture of natural progesterone and an estrogen is contacted with the skin of a patient suffering from dysfunctional bleeding. In another embodiment, the present invention provides a method for the treatment of corpus luteum failure in which a composition of the present invention comprising natural progesterone or a mixture of natural progesterone and an estrogen is contacted with the skin of a patient suffering from corpus luteum failure.

In another embodiment, the present invention provides a method for the treatment of post-menopausal senile vulvo-vaginitis in which a composition of the present invention comprising testosterone is contacted with the skin of a patient suffering from senile vulvo-vaginitis.

In another embodiment, the present invention provides a method for the treatment of hypogonadism in which a composition of the present invention comprising testosterone is contacted with the skin of a patient suffering from hypogonadism.

In another embodiment, the present invention provides a method for providing contraception in which a composition of the present invention comprising natural progesterone, synthetic progestins, estrogens or mixtures thereof is contacted with the

skin of a subject in need of contraception. The compositions of the invention may be sued to provide contraception to both males and females.

In the methods of this invention, the inventive composition comprising the appropriate hormone or hormone mixture is contacted with the subject's skin for a period of time sufficient to permit a therapeutically effective amount of the hormone or mixture of hormones to be absorbed through the skin into the subject's bloodstream.

The amount of progesterone in the blood which will be considered therapeutically effective will, of course, vary from patient to patient, and with the type of condition being treated. As a general rule, a therapeutically effective amount can be considered the level of progesterone one would anticipate during the second half of the luteal phase of the menstrual cycle. However, other levels produced by the normal functions of the body may also be effective, depending on the circumstances. For example, a mean serum level of 2 ng/ml progesterone gives an optimal effect in the treatment of menopause using a combination of progesterone and estrogen.

According to W.S. Maxon (1987, "Use of Progesterone in the Treatment of PMS," J. Clin. Obstetrics & Gynecology 30 (2): 465-480), the adrenal gland produces small amounts of progesterone from cholesterol and pregenelone as an intermediate in the biosynthesis of corticosteroids. During the proliferative phase of the menstrual cycle, most of the circulating progesterone is adrenal in origin and is produced in quantities of about 0.75 mg/day. During the follicular phase, serum concentrations of progesterone range between 0.1 and 1 ng/ml.

During the luteal phase, progesterone production by the ovarian corpus luteum dramatically increases and may reach 50 mg per day. When the conceptus is expected to implant during the mid-luteal phase, serum concentrations of progesterone average 5 to 25 ng/ml. Progesterone is released in a pulsatile fashion, which correlates with LH pulsatility. During pregnancy the placenta contributes an additional 25 to 40 mg/day of progesterone. Concentrations during gestation increase progressively to a mean of 175 ng/ml at term.

Thus, blood level of progesterone can fluctuate widely during the luteal phase of the cycle, i.e. at least from 0-50 ng/ml. Generally, however, the fluctuation is on the order of 0-18 ng/ml. The preferred method of assaying the level of progesterone in the

blood is by standard radioimmunoassay, which is well known to those skilled in the art.

Compositions of the present invention are also useful for treating vaginal conditions such as yeast infections and vaginal dryness. Compositions of the present invention are also useful as spermicides. For example, compositions of the present invention comprising a drug selected from butylurea and butaconazole can be used to treat vaginal yeast infections. Compositions of the invention comprising butylurea can also be used as spermicides. Compositions of the present invention, with or without drug(s), may be used to treat vaginal dryness.

Compositions of the present invention comprising progesterone, estrogen, progestin, testosterone and a mixture of any two or more of the foregoing may also be administered vaginally to treat a variety of vaginal or gynecological conditions.

Accordingly, the present invention provides methods for treating vaginal yeast infections. The present invention also provides methods for treating vaginal dryness. The invention also provides methods for contraception which involve the vaginal administration of compositions of the present invention comprising urea or urea derivatives such as butylurea. These methods involve the placement of a composition of the present invention inside the vagina of a subject.

## 6. EXAMPLES

### 6.1 MANUFACTURE OF A PREFERRED COMPOSITION OF THE INVENTION

A hydrogel-forming base mixture of the invention is prepared a by mixing together the following seven dry powder ingredients:

| | |
|---|---|
| 63% | methyl cellulose |
| 21% | guar gum |
| 5% | glucose |
| 3% | pectin |
| 1.5% | sodium chloride |
| 3.5% | propylparaben |
| 3% | methyl paraben |

After mixing the above ingredients, the mixture is micronized to a size of approximately one micron.

A composition for the transdermal delivery of natural progesterone containing the ingredients:

2% butylurea
9% base mixture hydrogel powder
10% progesterone
20% propylene glycol
59% distilled water

is prepared as described below.

Mix the hydrogel, butylurea and progesterone powders with the propylene glycol forming a paste. Warm (do not boil) the paste until the ingredients totally dissolve and the paste becomes a thinned pourable liquid. Use a large enough container to accept the combined volume of thinned paste and tepid water. Cold or hot water may be used to delay or accelerate the set-up time. Place the container with water in a stirring unit using a blade-type prop. Begin stirring water at a speed to form a vortex at the surface. Add all the combined warmed glycol mixture to the stirring water. Continue to mix for 3 to 15 minutes or until the proper or desired viscosity is achieved. Place a cover over the finished mixture to prevent short term evaporation. To prevent long-term evaporation, remove the finished mixture from the container and place in a vapor barrier container. Shelf life in the container should be several years.

## 6.2 SKIN PERMEATION ASSAYS: FULL THICKNESS HUMAN SKIN

### 6.2.1 MATERIALS AND METHODS

Materials

Excised full-thickness human skin was obtained from elective surgery, (e.g., breast reductions) or occasionally, from amputated legs. The tissue was stored in plastic containers at refrigerator temperature until use, at which time the subcutaneous fat and connective tissue were carefully trimmed off. Skin specimen thickness was in the range 1.5 - 2.0 mm, with characteristic histological features preserved.

Tritium-labeled progesterone was obtained from NEN-DuPont (Wilmington, DE), with the label at ring positions 1, 2, 6, and 7. It was incorporated in the test compositions in the range 100 to 500 DPM (Disintegration Per Minute) per microgram of progesterone. The labeled progesterone was incorporated at the pre-polymerization stage, i.e., just as water is added to form the hydrogel polymer. Aliquots of the gelling mixtures were added to small amounts of tritiated progesterone in scintillation vials (after the solvent had been evaporated), and stirred briskly with a small spatula. The

vials were then tightly capped and stored at room temperature. Milligram portions of this mixture were then taken from widely-spaced sites from within the vials, rapidly weighed, and dispersed in scintillation cocktail for determination of specific activities.

**Transdermal Penetration**

Transdermal penetration was performed in a single-chamber, solvent-replacement Diffusion Cell, held vertically and inverted (Figure 13). Half-inch diameter discs of skin to which nylon washers had been cemented with cyanoacrylate were used. The available diffusional area of each skin disc enclosed by the nylon washer was 0.495 $cm^2$. The cell was assembled from parts of a commercial PVC coupling manufactured by Genova Products, Inc., Davison, MI. The body of the coupling serves as the receptor chamber. The skin disc (5), kept flat by the nylon washer (6) cemented to its surface, is seated in the bottom end of the chamber, dermal side in contact with the receptor fluid (8). After test material is applied to the skin surface, an O-ring (4) and a flanged PVC washer (2) coated with aluminum foil (3) are positioned under the nylon washer on the skin, and a retaining nut (1) is carefully tightened under all. A small, teflon-covered magnetic stirring button (7) and the receptor fluid are introduced, after which the top end of the coupling is stoppered with another foil-coated flanged washer (9). After assembly, the cell is held in a rack on a magnetic stirrer, in a 32° C incubator. The magnetic stirring button is used to stir the receptor fluid in the inverted cell, and this button spins in direct contact with the dermal side of the skin. In this configuration, the 1 ml of fluid in the receptor chamber is mixed instantaneously as stirring is begun, and continuously during the course of the experiment. The receptor fluid was physiological saline, and 0.5 ml samples were removed (with replacement) at one-hour intervals.

**Intradermal Penetration**

Intradermal penetration was assessed with 0.5-inch diameter discs of skin, to which nylon washers were cemented, as described above. Discs with attached washers were placed in wells drilled in a plastic block. The block was then covered with a sheet of clear plastic to minimize dehydration of the skin. To terminate penetration, individual discs were removed from the block, and residual material removed from the surface by a rinse/wipe procedure as follows: 1) a stream of ice-cold water was delivered to the skin surface confined within the washer for 10 seconds, and the surface

then dried with absorbent paper. These steps were repeated, and then 2) a smaller disc of skin was punched out from within the cleansed area, and 3) dissolved for determination of tritiated progesterone. Dissolution was in 1N NaOH for an hour at 100° C followed by neutralization of the alkali solution with perchloric acid. If the epidermis was to be separated from the dermis for measurement of radioactivity, this separation was done by exposing the disc to an infrared heat lamp, held at 4 inches from the surface for 30 seconds, and peeling off the epidermis with fine forceps. Scintillation cocktail was added to the dissolved tissue samples, for determination of radioactivity.

Thirteen formulations were used in the Examples described hereinbelow. The formulations were prepared as described above by addition of radioactive progesterone during polymerization, before the final viscosity had developed. The thirteen formulations are give below. The hydrogel-forming base mixture used in all thirteen formulations consisted of: 63% methyl cellulose, 21% guar guam, 5% glucose, 3% pectin, 1.5% sodium chloride, 3.5% propyl paraben, and 3% methyl paraben.

| Sample A-1 | | Sample B-1 | | Sample C-1 | |
|---|---|---|---|---|---|
| 20% | propylene glycol | 20% | propylene glycol | 20% | propylene glycol |
| 4% | natural progesterone | 4% | natural progesterone | 4% | natural progesterone |
| 13% | hydrogel-forming base mixture | 13% | hydrogel-forming base mixture | 13% | hydrogel-forming base mixture |
| 3% | oleic acid | 3% | oleic acid | 3% | oleic acid |
| 60% | water | 59% | water | 59% | water |

| Sample A-2 | | Sample B-2 | | Sample C-2 | |
|---|---|---|---|---|---|
| 20% | propylene glycol | 20% | propylene glycol | 20% | propylene glycol |
| 4% | natural progesterone | 20% | natural progesterone | 20% | natural progesterone |
| 13% | hydrogel-forming base mixture | 13% | hydrogel-forming base mixture | 14% | hydrogel-forming base mixture |
| 3% | Myristic acid | 3% | Myristic acid | 1.5% | Myristic acid |
| 60% | water | 40% | water | 44.5% | water |

| Sample A-3 | | Sample B-3 | | Sample C-3 | |
|---|---|---|---|---|---|
| 20% | propylene glycol | 20% | propylene glycol | 20% | propylene glycol |
| 4% | natural progesterone | 4% | natural progesterone | 4% | natural progesterone |
| 13% | hydrogel-forming base mixture | 14% | hydrogel-forming base mixture | 14% | hydrogel-forming base mixture |
| 3% | n-butylurea | 6% | n-butylurea | 1.5% | n-butylurea |
| 60% | water | 56% | water | 60.5% | water |

| Sample W | Sample X |
|---|---|
| 20% propylene glycol | 20% propylene glycol |
| 5% natural progesterone | 10% natural progesterone |
| 13% hydrogel-forming base mixture | 13% hydrogel-forming base mixture |
| 1.5% n-butylurea | 1.5% n-butylurea |
| 60.5% water | 55.5% water |

| Sample Y | Sample Z |
|---|---|
| 20% propylene glycol | 20% propylene glycol |
| 15% natural progesterone | 20% natural progesterone |
| 11% hydrogel-forming base mixture | 9% hydrogel-forming base mixture |
| 1.5% n-butylurea | 2.5% n-butylurea |
| 52.5% water | 48.5% water |

### 6.2.2 PROGESTERONE PENETRATION THROUGH A DIALYSIS MEMBRANE

Since the transdermal progesterone experiments were to be performed using physiological saline as the receptor fluid, it was first determined if penetration might be limited by solubility of progesterone in the physiological saline. Thus, penetration of progesterone through a dialysis membrane, which was assumed to be more permeable than the skin, was measured to see how much progesterone could accumulate in the receptor of the diffusion cells. The dialysis membrane used was Spectra/Por$^R$ No. 1 dialysis tubing, purchased from Thomas Scientific, Swedesboro, NJ. The dialysis

membrane was positioned in the diffusion cell as described above. The results are given in Figure 14, which is a plot of the cumulative amount of progesterone penetrated ($\mu g/cm^2$) over a period of about 1.5 hours. Figure 14 shows that penetration occurred at a rate of about 30 $\mu g/cm^2/Hr$. Note that there appeared to be no lag time, i.e., the rate of penetration appeared to be linear from the time of contact. Such a time course for penetration is consistent with diffusion through pores (i.e., the solvent-filled pores of the dialysis membrane).

### 6.2.3 TRANSDERMAL PENETRATION OF PROGESTERONE: COMPARISON OF COVERED AND NOT-COVERED SAMPLES

Using Sample A-1, rates of progesterone penetration through the skin were compared for covered with a layer of aluminum foil vs. not-covered samples. Figure 15 shows a plot of the cumulative amount of progesterone penetration ($\mu g/cm^2$) over a period of about 8 hours for uncovered and covered samples of A-1. Clearly, penetration proceeds more rapidly through the skin when the application site is covered. Also note that there is a lag time, i.e., the steady-state rate of progesterone penetration was not established until 2-3 hours after application. This kind of time course is consistent with the drug having to partition into (dissolve in) the skin before the transdermal diffusional process begins.

### 6.2.4 TRANSDERMAL PENETRATION OF PROGESTERONE: COMPARISON OF OLEIC ACID, MYRISTIC ACID AND BUTYLUREA PENETRATION ENHANCERS

Rates of transdermal penetration of progesterone were determined for three samples: A-1, A-2, and A-3. Each of these samples was of the same viscosity, but each contained a different kind of penetration enhancer. (The compositions of these samples are given above in Section 6.2.1). The penetration data for samples A-1, A-2 and A-3 are given in Table 1.

**Table 1. Transdermal Penetration of Progesterone**
**$\mu g/cm^2$**

**Sample A-3**

| | Hrs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Skin | #1 | 1.3 | 3.9 | 9.2 | 18.0 | 28.0 | 37.4 | 48.2 | 57.6 |
| Skin | #2 | 0.49 | 5.8 | 14.8 | 28.6 | 46.0 | 63.7 | 82.9 | 105.2 |
| Skin | #3 | 4.5 | 13.3 | 25.0 | 37.1 | 49.8 | 63.7 | 77.0 | 92.3 |

Steady-state Rates, $\mu g/cm^2$/HR: #1 = 9.8, #2 = 18.1, #3 = 13.4

**Sample A-2**

| | Hrs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Skin | #1 | 0.29 | 0.97 | 1.8 | 4.1 | 5.6 | 7.7 | 9.7 | 11.5 |
| Skin | #2 | 0.35 | 1.2 | 2.6 | 5.1 | 8.0 | 11.3 | 14.6 | 18.9 |

Steady-state Rates, $\mu g/cm^2$/HR: #1 = 1.9, #2 = 3.2

**Sample A-1**

| | Hrs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Skin | #1 | 0.53 | 1.4 | 2.9 | 5.4 | 8.7 | 11.9 | 14.6 | 18.4 |
| Skin | #2 | 3.4 | 7.9 | 12.6 | 16.9 | 21.8 | 26.4 | 31.1 | 36.3 |

Steady-state Rates, $\mu g/cm^2$/HR: #1 = 1.9, #2 = 3.2

As may be seen in Table 1, n-butylurea was clearly the most efficacious of the three in promoting the penetration of progesterone through the skin. The highest rate observed, (18.1 $\mu g/cm^2$/Hr, sample A-3, skin #1) was for the composition of the present invention containing n-butylurea.

Note that the rate of 18.1 $\mu g/cm^2$/Hr was substantially lower than that measured through dialysis membrane (Section 6.3.2). Thus, the test system does not impose an upper limit on the rate of penetration, and therefore, the measured rates are a true indication of how fast the drug can be transferred through the skin from these formulations.

Some of the data from these determinations are plotted in Figure 16, to illustrate how the rates were determined. A linear regression analysis was performed for each of

the three curves, corresponding to samples A-1, A-2 and A-3, respectively, using the points taken in the interval from 3-8 hours. The rates were derived from the slopes of the curves. The rate is defined as the slope of the plot of the cumulative amount of progesterone penetrated in $\mu g/cm^2$, versus time in hours. It may be seen that the plots are almost perfectly linear during this interval (regression coefficient > 0.99). The position of the x-intercepts indicates that there was a lag time of about two hours. Table 3 gives the 3-8 hour steady state rates, the average for hours 1-8 of penetration and the average rates for hours 8-30 of penetration for samples A-1, A-2 and A-3. It is also clear from the data in Table 2 that the rate of penetration measured in the first eight hours of contact with the skin was sustainable for more than a day (30 Hrs in this experiment).

**Table 2**
**Maintenance of the Rate of Progesterone Penetration ($\mu g/cm^2/Hr$)**
**(Skin #1)**

| | Steady-state, 3-8 Hrs | Av. Rate, 1st 8 hrs | Av. Rate, 8-30 Hrs |
|---|---|---|---|
| A-1 | 3.1 | 3.3 | 1.2 |
| A-2 | 1.9 | 1.7 | 1.6 |
| A-3 | 9.8 | 9.1 | 8.9 |

* Skin Donor Number, #1, #2, etc.

### 6.2.5 INTRADERMAL PENETRATION OF PROGESTERONE; COMPARISON OF OLEIC ACID, MYRISTIC ACID AND BUTYLUREA PENETRATION ENHANCERS

Since it had been observed that dilution of the receptor fluid seemed to decrease transdermal penetration, samples A-1, A-2, A-3, B-1, B-2, B-3, C-1, C-2, and C-3 were compared by measuring intradermal penetration rather than transdermal penetration. The observed dilution-dependent decrease in transdermal penetration was contrary to expectation, since normally, lowering drug concentration the receptor increases penetration, as it increases the concentration gradient across the skin. The decrease was especially unexpected because in this model, the receptor volume is at a minimum (only the fluid in the dermal compartment of the skin).

All measurements were performed on skin from a single donor. Results are given in Table 3.

**Table 3. Intradermal Penetration of Progesterone, over 20 Hrs, $\mu g/cm^2$**

| Sample | Full-thickness | Dermis |
|---|---|---|
| A-1 | 71.4 | 36.3 |
| A-1* | 47.3 | 29.0 |
| A-2 | 72.6 | 33.6 |
| A-3 | 44.5 | 34.0 |
| B-1 | 91.0 | 19.6 |
| B-2 | 59.1 | 40.0 |
| B-3 | 54.5 | 37.0 |
| C-1 | 50.5 | 33.0 |
| C-2 | 71.0 | 619.6 |
| C-3 | 56.5 | 27.6 |
| Mean, +/- SD | 61.8, +/-14.4 | 31.0, +/-7.0 |

As Table 3 shows, a mean value of about 60 $\mu g/cm^2$ could be recovered from "full thickness" skin after a 20-hr contact period, and about 30 $\mu g/cm^2$ from the dermal portion of the skin, the site of the dermal capillary network. These numbers indicate that only about 3 $\mu g/cm^2$/Hr penetrated the skin when there was no added receptor fluid in contact with the dermis, and that about half the penetrating material actually got into the dermis, i.e., under these circumstances, about 1.5 $\mu g/cm^2$/Hr of progesterone was "available" for uptake into the capillaries. Further, the rate of differences observed with different enhancers in the first set of comparisons (Section 6.2.4, Table 1, Figure 16), could not be demonstrated.

### 6.2.6 TRANSDERMAL PENETRATION OF PROGESTERONE: COMPARISON OF OLEIC ACID AND BUTYLUREA PENETRATION ENHANCERS

Transdermal penetration using samples A-3 and C-3 was measured using skin from the same donor as was used in Section 6.3.5. Measurements were performed in two ways: with the sampling from the diffusion cells during the first eight hours, and without such sampling (Table 4). In this experiment, the amounts that passed through the skin were much higher when the diffusion cells were not sampled, however the best

hourly average for transdermal penetration rate (Sample C-3, 4.8 $\mu g/cm^2/Hr$), was still only about one-half the lowest rate measured with n-butylurea in Section 6.2.4 (Table 1).

**Table 4. Transdermal and Intradermal Penetration of Progesterone over 20 Hrs, $\mu g/cm^2$**

| | A-3 | A-3** | C-3 | C-3** |
|---|---|---|---|---|
| Transdermal | 36.0 | 56.0 | 28.1 | 95.5 |
| Intradermal, Dermis | | 23.0 | | 81.4 |
| Intradermal, Epidermis | | 18.6 | | 20.3 |

* A duplicate of sample A-1.
** These cells were not sampled, whereas the other member of each pair, (A-3 and C-3) were sampled during the first eight hours.

### 6.2.7 TRANSDERMAL PENETRATION OF PROGESTERONE USING BUTYLUREA PENETRATION ENHANCER: COMPARISON OF VISCOSITIES

To access the effect of viscosity on transdermal penetration rate, rates were measured using samples of low viscosity (A-3) and high viscosity (C-3), both containing n-butylurea. The results, presented in Table 5, indicated that in the range tested, viscosity did not affect the transdermal penetration rate. It is also clear that penetration rates through these skin samples (average 9-10 $\mu g/cm2/Hr$) were higher than the best rate shown in Table 4, providing some indication that the skin used in Section 6.2.5 for measurements of intradermal penetration and in Section 6.2.6 for transdermal penetration may have had atypically low permeability.

**Table 5. Transdermal Penetration Progesterone, $\mu g/cm^2/Hr$ (20-Hr Assay, w/ Hourly Sampling)**

| Test Article | A-3 | | C-3 | |
|---|---|---|---|---|
| Skin # | I | II | I | II |
| | 7.8 | 10.4 | 8.9 | 11.2 |
| | 9.4 | 11.9 | 6.7 | 11.4 |
| | 7.2 | 9.5 | 9.8 | 10.0 |
| Mean SD | 8.13 | 10.56 | 8.47 | 10.87 |
| | 1.14 | 1.16 | 1.59 | 0.75 |
| Mean, All Samples SD | | 9.35 | | 9.67 |
| | | 1.68 | | 1.72 |

### 6.2.8 TRANSDERMAL PENETRATION OF PROGESTERONE: EFFECT OF PROGESTERONE CONCENTRATION

To access the effect of progesterone content of the inventive compositions upon transdermal penetration, tests were carried out using samples W, X, Y and Z in which the progesterone concentration was varied from 5 to 20%. The results are give in Table 6.

**Table 6. Transdermal Progesterone Penetration. Initial and Sustained Rates, in $\mu g/cm^2/Hr$**

| Skin No. | | I | | | II | III |
|---|---|---|---|---|---|---|
| Rate | | Initial | 0-24Hr | 24-48Hr | Initial | Initial |
| Sample | Progesterone Conc., (%) | | | | | |
| W | 5 | 5.2 | 4.9 | 5.0 | 4.7 | 6.2 |
| X | 10 | 6.7 | 6.1 | 6.0 | 5.8 | 8.1 |
| Y | 15 | 7.8 | 7.0 | 7.3 | 6.5 | 9.0 |
| Z | 20 | 11.1 | 10.4 | 10.0 | 10.5 | 13.6 |

As may be seen in Table 6, a 4-fold increase in concentration resulted in a doubling of the penetration rate, both initially, and in the rate sustainable for up to 48 hours. While the concentration dependency appears to be real, it should be noted that the highest rate observed here (about 14 $\mu g/cm^2/hr$) was not higher than the 18.1 $\mu g/cm^2/Hr$ rate seen

with a 4% progesterone formulation in Section 6.2.4 (see Table 1). This disparity may be due to skin-to-skin variation.

### 6.2.9 TRANSDERMAL PENETRATION OF PROGESTERONE: COMPARISON OF FULL-THICKNESS SKIN AND SKIN FROM WHICH THE EPIDERMIS HAD BEEN REMOVED

The transdermal penetration of the progesterone through full-thickness skin was compared to penetration through skin from which the epidermis had been removed. The rate increased only about 2-fold after this maneuver, indicating that the dermis is an important factor in limiting the rate of penetration through the skin.

## 6.3 DEMONSTRATION OF INTRADERMAL PENETRATION OF PROGESTERONE BY AUTORADIOGRAPHY

Introduction

It was not possible to demonstrate progesterone within the skin by conventional histological techniques, as it appeared to be extracted by the alcohols used in processing. Therefore, an alternative procedure was used to acquire skin surface biopsies (Marks and Dawber, 1971, Brit. J. Dermatol. 85:117-123). Surface biopsies consist of a sheet of the top 2-3 layers of the stratum corneum, which retain vellus hairs on the underside, along with fragments of the pilosebaceous ducts known as "follicular casts" (Lavker and Leyden, 1979, "Lamellar Inclusions in Follicular Horny Cells: A New Aspect of Abnormal Keratinization," J. Ultrastruct. Res. 69: 362-370). These samples are produced by application of a drop of cyanoacrylate adhesive on a microscope slide to the surface of the skin, and after the adhesive sets, the slide with adhering tissue is carefully peeled off. When surface biopsy samples were taken from skin to which radioactive progesterone had been applied, a time-dependent accumulation of progesterone in the tissue could be demonstrated, by autoradiography.

Procedure

Discs of skin were prepared as described in "Methods", for measurement of intradermal penetration, but using much larger washers to provide test sites of about 10 $cm_2$ in area. A test formula containing 20% progesterone (Sample Z) was applied, and

uptake into the skin was allowed to proceed for one hour, and for 20 hours. Surface residue was removed at the indicated times, using the rinse/wipe procedure described. Skin surface biopsies were taken from 1 & 20-Hr skin discs, and coated with photographic emulsion (Illford K-2 emulsion, Illford, London), then allowed to develop for 14 days. Rinsing and fixing were done as prescribed by the manufacturer.

Results

Three surface biopsies were photographed with black-and-white film, on a white background, with sub-surface illumination. There was a distinct gradation in grayness, increasing from the baseline level of the control sample to the 20-Hr sample, as would be expected with increasing numbers of silver grains. It is clear that the stratum corneum as a whole darkened with time, but the follicular fragments were much darker than the interfollicular stratum corneum, indicating a preferential accumulation of progesterone in the pilosebaceous follicles. This pattern was also obvious when sections were photographed with incident light. Ridges and grooves that crisscrossed the undersurface were visible; these are the "negative" of the fine folds on the surface of the skin. A high magnification study of the sections was undertaken, to establish that the pattern of darkness, or opacity, seen in these low-magnification images was really due to silver grains. A view of the underside of a control biopsy, showed an uprooted vellus hair enveloped by a mixture sebum and compacted corneocytes (keratinized stratum corneum cells). It resembled a horn with a collar, emerging from the background undersurface of the stratum corneum.

The horn is the coated hair, and the collar a portion of the infundibulum, or funnel-shaped opening of the pilosebaceous duct, that emerges on the surface of the skin. The polygonal outlines of individual corneocytes are sometimes discernible, a convenient metric (about 40 microns) for the scale of the images. In distinct contrast to a control section, the underside of a section from skin which had been in contact with a tritiated 20% progesterone formula for 20 hours appeared to be stained a deep blue color, most intensely at follicular structures. At higher magnification, the blue stain could be resolved into individual silver grains, seen as a stippling of blue dots about 500 nanometers in diameter. Where the wall of the follicle was perpendicular to the plane

of the section (W), the stain was much more intense, a combination of a higher grain density, and effectively viewing a thicker section (imagine looking at the edge of a piece of stained glass). An image of a 0.2 mm-long follicular fragment showed that progesterone was distributed uniformly to this depth within the lipid-rich interior of the follicle. Finally, stippling (and thus silver grains) was absent from a control biopsy, taken from tissue which had never been in contact with radioactive material.

Summary

The disposition of tritiated progesterone in the surface biopsies examined is consistent with diffusion through the follicles, as well as diffusion through the interfollicular stratum corneum. Accumulation in the follicles appeared to be faster than in the stratum corneum, but both were shown to be time-dependent. The contribution of each route to the combined rate of penetration is not easily determined, but it should noted that the surface area of the openings of the follicles is estimated to be only about 0.001% of the area in contact with the applied test formulation (about 30 follicles per $cm^2$, and about 100 $micron^2$ per follicle). To have a real impact under these circumstances, movement through the follicular "shunt" route would have to be more than four orders of magnitude faster, per unit area. If, however, we invoke the length of the follicular shunts, the real interfacial area (follicle/dermis) could approach 1%, and under these circumstances, if the transfer rate from follicle to dermis were only 10 times as fast (or more) as the transfer rate from stratum corneum to dermis, then the shunt route could approach or even exceed the contribution of the transepidermal route to the total rate of penetration.

The Examples above demonstrate that progesterone penetration rates using compositions of the present invention are in the range 1-20 $\mu g/cm^2/hr$, and appear to be sustainable for at least 48 hours (Table 6). The rate at the higher end of this range is in excess of two orders of magnitude greater the 1.2 $\mu g/cm^2/day$ rate reported by Guy et al., (1987, "Kinetics of Drug Absorption Across Human Skin In Vivo," Pharmacol. Skin 1: 70-76). (discussed *supra*). Although Barry and Bennett, (1987, "Effect of Penetration Enhancers on the Permeation of Mannitol, Hydrocortisone, and Progesterone Through Human Skin," J. Pharm. Pharmacol. 39: 535-546), reported somewhat higher rates when certain permeation enhancers were used (*supra*), that

method of application increases delivery by pretreatment of skin with acetone and thus that method of application to the skin is not amenable to a transdermal delivery patch system. Thus, the compositions of the present invention provide unexpectedly superior delivery to the blood of the hormone contained within them and a very promising aspect of a sustained-released transdermal delivery system for progesterone.

## 6.4 SKIN PENETRATION ASSAYS: HUMAN EPIDERMAL MEMBRANES

### 6.4.1 BACKGROUND AND SUMMARY

In these experiments, a revised *in vitro* percutaneous absorption model was used. The appropriateness of full thickness skin as a diffusional barrier, the radioactive labeling of test formulations after they had been compounded, and establishing the identity of the radioactive species in the receptor of the diffusion cell after diffusion has occurred were addressed. These issues were dealt with as follows:

1. Heat-separated human epidermal membranes were used instead of full-thickness human skin.
2. The test formulations were compounded with progesterone which had been radiolabeled by mixing tritiated progesterone with "cold" progesterone dissolved in propylene glycol at 100 °C.
3. The radioactive species in the receptor of the diffusion cell was extracted from the saline receptor fluid, and shown by thin layer chromatography to be indistinguishable from the progesterone which had been applied to the surface of the skin.

Two progesterone formulations were tested, one with 2% enhancer (Test Formulation A-4) and one with 4% enhancer (Test Formulation B-4). Mean penetration rates of 3.2 and 6.1 micrograms per centimeter squared per hour were determined, for the 2% and the 4% enhancer formulations, respectively (see Figure 21). These results indicate that 1-1.5 mg (0.77-1.46 mg) per day can be delivered to the body, from a 10 $cm^2$ patch, and that the penetration rate can be modulated by varying the concentration of enhancer. Of particular interest is Test Formulation A-4, which is the same formula used in the *in vivo* study described in Section 6.5. Impressive (clinically significant) serum and saliva levels were achieved when Formulation A-4 was applied to human test subjects

during a single 8-hour application using a 10 x 10 $cm^2$ patch. It is likely that concentrations observed *in vitro* could rise substantially, with continuous *in vivo* application of a patch, using an optimized formula (e.g., with higher enhancer concentration). In such instance, the patch could be reduced in size to something which could be worn around the wrist, or applied at some other convenient body site.

Test formulations A-4 and B-4 had the following compositions:

| A-4 | | |
|---|---|---|
| Natural Progesterone | 0.200 g | (16.3 wt %) |
| Propylene Glycol | 0.200 g | (16.3 wt %) |
| Butylurea | 0.025 g | (2.0 wt %) |
| Polymer | 0.090 g | (7.3 wt %) |
| Distilled Water | 0.71 g | (58.0 wt %) |

| B-4 | | |
|---|---|---|
| Natural Progesterone | 0.195 g | (15.7 wt %) |
| Propylene Glycol | 0.194 g | (15.7 wt %) |
| Butylurea | 0.050 g | (4.0 wt %) |
| Polymer | 0.090 g | (7.3 wt %) |
| Distilled Water | 0.71 g | (57.3 wt %) |

The polymer (hydrogel-forming base mixture) was composed of the following ingredients: 63% methyl cellulose, 21% guar gum, 5% glucose, 3% pectin, 1.5% sodium chloride, 3.5% propyl paraben and 3% methyl paraben.

### 6.4.2 MATERIALS AND METHODS

**Preparation of Epidermal Membranes:** All membranes used in this series of experiments were isolated from skin samples obtained after breast reduction. Donors were Caucasian females, ages 26-48. The epidermis was peeled from the dermis after the skin had been immersed in distilled water at 60°C, as described by R.J. Scheuplein (1986, "Mechanism of Percutaneous Absorption," J. Invest Dermatol. 45:334-346). The membranes were spread corneum-side down on aluminum foil, and stored over

Drierite at room temperature. In this desiccated state they are brittle, and they were therefore carefully dehydrated before discs of tissue were punched out for placement on the diffusion cells.

**Diffusion Cell Design and Assembly:** Transepidermal penetration was measured using single chamber diffusion cells. The diffusion cell described in Section 6.2 was redesigned to work with epidermal membranes, which are much thinner and more fragile than the full-thickness skin from which they are isolated. For parts, the same polyvinyl chloride ("PVC") couplings described in Section 6.2 were used to make a donor assembly (Figure 20) which could be partially immersed, so that the underside of the epidermal membrane was in contact with saline held in a glass receptor. A half-inch diameter epidermal membrance disc was positioned such that its dermal surface was in contact with normal saline (2.5 ml) held in a glass receptor. The diffusion area was 0.71 $cm^2$. The saline was stirred continuously using a small stirring bar. Diffusion cells were incubated at 32°C. The cells were covered with a plastic sheet to prevent evaporation from the receptor.

At each time point, a 0.5 ml aliquot of receptor fluid was removed and replaced with an equal volume of normal saline, prewarmed to 32°C. Progesterone penetration was estimated by measuring the amount of tritiated progesterone contained in each aliquot, using standard techniques. Plots of the cumulative amount collected in the receptor with time were used to determine progesterone penetration rates, expressed in $\mu g/cm^2$/hour (see Figure 21). Four separate determinations were made for each of the two formulations tested. The extracted labeled material was shown by thin layer chromatography to be indistinguishable from fresh natural progesterone.

The membranes were examined visually with a hand lens before each experiment, to confirm that no visible defects were present. Following each experiment, Blue Dextran (molecular weight 2 million, obtained from Pharmacia Biotech) solution was added to the epidermal side of the membrane. There was no leakage of the Dextran into the receptor fluid after 24 hours.

As shown in Figure 21, formulations A-4 and B-4 resulted in steady-state, linear penetration of natural progesterone through human epidermal membranes, following a

lag time of about 1 hour. Formulation A-4, which contained 2% butylurea, had a steady state penetration rate of 3.2 $\mu g/cm^2/hr$, while formulation B-4, which contained 4% butylurea, had a steady state penetration rate of 6.1 $\mu g/cm^2/hr$.

**Compounding and Radiolabeling of Test Formulations A-4 and B-4.** Tritiated progesterone was purchased from NEN-Dupont (96 Ci/mmole), and was labeled in ring positions 1, 2, 6, and 7. Compounding was as follows:

1. "Cold" progesterone (i.e., non-radioactive progesterone), radioactive progesterone, and propylene glycol were mixed in a small screw-cap vial, which was immersed in boiling water for 5-10 minutes, until an optically clear solution was obtained. The vial was removed from the bath and allowed to cool for 2 minutes, then added all at once to an aqueous mixture described in no. 2 below.

2. Enhancer was dissolved in an appropriate volume of water, in a heavy 2-ounce "shot glass", stirred with a straight steel rod at 1500 RPM. A weighed amount of polymer was then dusted onto the vortex of stirring solution, to ensure rapid, thorough mixing. As soon as thickening was evident, the progesterone-glycol solution from No. 1 above was added, and the stirring rate increased to 3000 RPM. Stirring was continued for 2-3 minutes, until the mixture was the consistency of dough, and adhered to the rod; then the stirrer was turned off. With the help of a small spatula, the labeled polymer mixture was transferred to a clean scintillation vial, which was then tightly capped. The final mixtures had 5-600 dpm/microgram of hormone.

**Chromatographic Analysis of Progesterone:** Thin layer chromatography (TLC) of progesterone mixtures was performed on 250-micron silica gel GF plates (Analtech, Newcastle, DE) using a 1:1 mixture of cyclohexane and ethyl acetate as solvent. This system was recommended by NEN-Dupont. The plates were developed for about 30 minutes. Visualization of the chromatographed material was with short-wave UV, as the silica on the TLC plates contained a bound fluor, which was quenched by the UV-absorbing progesterone.

A stock solution of "cold" progesterone was prepared at 1 mg/ml in ethyl acetate. Five-μl aliquots of this solution (about 50 μg) were spotted and run as described. After drying, UV examination disclosed a single spot, with an $R_f$ of 0.68.

Fifty mg of Test Formulation A-4 was extracted with 1 ml of ethyl acetate and 5-μl aliquots spotted for analysis. These aliquots also yielded a single spot on visualization, with an $R_f$ that was indistinguishable from that obtained with the "cold" stock solution. When the spots were scraped from the TLC plate and suspended in scintillation cocktail, spuriously high counts were observed because of the fluor bound to the silica gel. These counts were found to decrease as the silica settled, but as this procedure was time-consuming, the practice was adopted of centrifuging the suspension at 1000xg for 5 minutes and counting the supernatant. As may be seen in Table 9, this procedure resulted in an apparent loss of counts (14%), which was significant, but reproducible. We were unable to detect radiolabel elsewhere on the track of the migrating progesterone, thus the loss is probably due to absorption of progesterone in the pelleted silica gel. (We also found that adding increasing amounts of silica to "hot" (radioactive) progesterone dissolved in scintillation cocktail resulted in increasing losses of radioactivity in the supernatant after centrifugation).

Receptor fluid (2.5 ml) was removed from an assembled diffusion cell about 5 hours after Test Formulation A-4 had been applied. This fluid was extracted with 5 ml of ethyl acetate with vigorous shaking for 10 minutes. Five-μl aliquots were counted or applied to a TLC plate to assess their identity and purity. On visualization with UV after the plates were developed, three UV-absorbing spots could be detected, one with $R_f$ 0.68. As may be seen in Table 10, about 75% of the applied counts were recovered in this "progesterone spot". No radioactivity could be detected in the other UV-absorbing spots, or elsewhere on the TLC plate. The apparently lower percent recovery in the "progesterone spot" in this experiment vis-à-vis the recovery observed for the Test Formulation extract (see Table 9) is probably due to the fact that a smaller amount of material was spotted on the TLC plate.

### 6.4.3 RESULTS AND DISCUSSION

In Section 6.2 skin penetration of progesterone was assessed by measuring transdermal penetration rates; in this section, transepidermal penetration rates are described. Similar to the earlier measurements, a steady-state rate of penetration was established within the first several hours of contact (Figure 21). The lag time was somewhat shorter, as might be expected for a thinner diffusional barrier. The rates (Table 7) are lower than those reported in Section 6.2, probably because the radioactive progesterone is now mixed with insoluble as well as soluble progesterone, whereas in the Section 6.2 experiments, only the soluble portion of the progesterone was labeled, resulting in penetration values.

When the concentration of enhancer was doubled (Table 8), the rate increased proportionately, i.e., a approximate doubling of the rate.

Heating the progesterone in propylene glycol resulted in a true solution of the hormone, thus assuring a thorough mixing of the radioactive and non-radioactive forms. A possible consequence of this heating was some decomposition of progesterone. We have checked this as follows:

Thin-layer chromatography (TLC) of the progesterone supplied by the manufacturer yielded only a single spot on the TLC plate, with an $R_f$ of 0.68. When Test Formulation compounded with heated "hot" and "cold" progesterone was extracted with ethyl acetate, one of the chromatographic solvents, the extract also yielded a single spot on the TLC plate, with an $R_f$ identical to the original material, and all the radioactivity recoverable from the TLC plate was confined to this spot; Table 9. This means that the heating did not cause any discernible alteration of progesterone and that the "hot" progesterone is identical to the "cold".

To establish the identity of the radiolabeled species in the receptor of the diffusion cell, receptor fluid was extracted with ethyl acetate after five hours of transepidermal penetration. This ethyl acetate extract was concentrated and then spotted on a TLC plate. Visual examination of the TLC plate then showed three spots, one of which was at $R_f$ 0.68. All of the radioactivity recoverable from the TLC plate was

(Table 10) again confined to this "progesterone spot." It thus appears that little chemical or enzymatic changes occur when progesterone passed through the epidermis, and that tritium in the receptor is a true indicator of progesterone penetrating.

**Table 7**

**Progesterone Penetration through Epidermal Membranes from 3 Different Skin Samples ($\mu g/cm^2/hr$) Test Formulation A-4**

| | Skin I | Skin II | Skin III |
|---|---|---|---|
| | 3.6 | 3.9 | 4.1 |
| | 3.3 | 3.4 | 4.5 |
| | 3.1 | 3.6 | 4.8 |
| | 2.7 | | 3.8 |
| Mean | 3.2 | 3.6 | 4.3 |

**Table 8**

**Effect of Enhancer Concentration on Transdermal Penetration of Progesterone ($\mu g/cm^2/hr$)**

| | Test Formulation A-4 | Test Formulation B-4 |
|---|---|---|
| | 3.6 | 7.7 |
| | 3.3 | 6.3 |
| | 3.1 | 5.6 |
| | 2.7 | 4.7 |
| Mean | 3.2 | 6.1 |
| S.D. | 0.378 | 1.266 |
| B > A; 99.99% | (P < 0.001) | |

Note: Four replicate determinations using membranes from a single skin sample obtained after breast reduction from a Caucasian female.

**Table 9**

**Ethyl Acetate Extract of Test Formulation A-4**
**Recovery of Tritium at TLC Progesterone Spot**

| | | | | | | MEAN |
|---|---|---|---|---|---|---|
| DPM/5μl* | 27,986; | 28,783; | 28,331; | 28,414; | 28,269 | 28,339 |
| DPM/Progesterone Spot** | 24,310; | 25,083; | 23,993; | 24,690; | 25,514 | 24,318 |

* Five-μl aliquots of extract (containing about 38 micrograms of progesterone) were added to scintillation-counting vials containing 10 ml of cocktail.

** Five-μl aliquots of the same extract were spotted on a TLC plate, which was developed for 30 minutes. After drying, the spot at $R_f$ 0.68 was scraped off and added to 10 ml of cocktail. Samples were counted after the silica gel particles were removed by centrifugation, as described.

Note: "DMP" refers to "Disintegrations Per Minute", which is a measure of radioactivity.

**Table 10**

**Ethyl Acetate Extract of Diffusion Cell Receptor Fluid:**
**Tritium Recovery at TLC Progesterone Spot**

| | | | | MEAN |
|---|---|---|---|---|
| DPM/5μl* | 1207 | 1241 | 1086 | 1178 |
| DPM/Progesterone Spot | 848 | 966 | 821 | 878 |

* After about 5 hours of diffusion, the receptor fluid (2.5 ml) from a diffusion cells was extracted with 5 ml of ethyl acetate, and concentrated to about 100 μl. Five-μl aliquots were added directly to scintillation cocktail and counted, or spotted on a TLC plate. DPM in the second line of the Table represent the amount of progesterone recovered from the "Progesterone Spot" ($R_f$ 0.68). UV-absorbing material appeared at two other spots on the TLC plate, but these were found to be non-radioactive.

## 6.5 IN-VIVO STUDY OF TRANSDERMAL PENETRATION OF NATURAL PROGESTERONE

### 6.5.1 BACKGROUND AND SUMMARY

This study was designed to measure the *in-vivo* transdermal penetration of progesterone using compositions of the present invention. Serum and saliva sampling were elected as the cardinal indices of absorption. Urinary excretion of progesterone and its by-products are not a reliable index of total progesterone excretion, due to difficulties in analysis, and also because large amounts of progesterone are excreted into the bile. Measurement of salivary progesterone has an advantage over other assays because it represents free unbound progesterone.

Three male candidates were chosen for this study. Males were selected for the study because only small amounts of progesterone are made in the adrenal cortex and in the testes.

### 6.5.2 MATERIALS AND METHODS

Studies were carried out under the guidelines of the Midtown Hospital (Atlanta, Georgia) human studies committee, following review and approval of the study protocol. Three normal males, ages 30, 40 and 49 were selected and informed consent was obtained. The subjects for the study were in good health and were screened to confirm that each was free of any known medical problems and not taking any medications.

The transdermal progesterone formulation used in this study was the same as Test Formulation A-4, described in Section 6.4, supra, except that the formulation used in this study did not contain radioactive progesterone.

Just prior to application, approximately 45 g of the formulated material was applied in a thin layer to a 100 $cm^2$ square piece of plastic to form a crude patch. The site of application for the transdermal progesterone formulation was on the skin overlying the pectoral muscle. The skin was prepared by gently shaving the existing hairs. The plastic patch receptacle containing the test formulation was applied to the skin and taped in place. The system had no external pressure applied to the surface of the receptacle.

Prior to the initiation of the study, baseline saliva and serum levels of progesterone were obtained from the candidates. Subsequent sampling was at 24 and

48 hours. Serum was obtained by venipuncture. Saliva was collected by asking the subjects to expectorate into a sterile plastic container. The serum progesterone concentration was determined by SmithKline Laboratories, Atlanta, Georgia, using a standard clinical radioimmunoassay. Salivary progesterone assay was performed by Aeron Life Cycles, San Leandro, California. Aeron has considerable experience in the measurement of compounded natural progesterone products in saliva. In test populations previously studied by Aeron, males and postmenopausal females have basal salivary progesterone levels of <0.05 ng/ml, while that of premenopausal females ranges from 0.05 to 0.5 ng/ml.

During the test period, subjects rested in the semisupine position, so as not to disturb the patches. Lunch was provided. Patches were applied between 8:30 and 9:30 AM and removed after 8-9 hours. Following patch removal, the remaining formulation was removed by gently washing the area with water. Skin was blotted dry with soft paper tissue. Subjects went home and returned on each of the following two mornings to provide the 24 and 48 hour samples.

Baseline progesterone ranges in both saliva and serum in men normally range from 0.02 to 0.05 nanograms per ml. The reason salivary levels of progesterone were chosen for measurements is that salivary levels reflect the free plasma fraction. Many factors may alter the level of binding proteins in the blood or affect the binding of steroids to them. This greatly complicates the interpretation of the total plasma steroid levels. Serum measurement of total progesterone must therefore be interpreted with caution. These considerations are not a significant problem in the current study, however, since the concentration of progesterone binding proteins would not be expected to change during the brief duration of the of the experiment. Saliva samples avoid these problems by giving an index of the free plasma level.

The lipid, soluble, unconjugated steroids (such as cortisol, estriol, testosterone, progesterone, etc.,) enter saliva predominantly via the intracellular route. Their salivary concentrations are not dependent on saliva flow rate, and their salivary concentrations closely approximate their unbound concentration in plasma. Unconjugated steroids enter saliva by diffusing through the cells of the saliva glands and their concentration in saliva does not depend on the rate of saliva production. Both the saliva progesterone assay

and serum assays for progesterone were performed by radioimmunoassay which uses the competition between radioactive and non-radioactive progesterone for a fixed number of antibody binding sites to determine the progesterone concentration present in the specimen.

### 6.5.3 RESULTS

Transdermal delivery of natural progesterone was assessed in three male volunteers by measurement of serum and salivary progesterone levels, at time points ranging from zero to 48 hours following patch application. The serum progesterone data is shown in Table 11 and the saliva progesterone data is shown in Table 12. All three men showed baseline serum levels of 0.4 ng/ml and saliva values of 0.04, 0.04 and 0.02 ng/ml, consistent with established normal values in men.

Although the *in-vivo* transdermal penetration study described herein used an unsophisticated receptacle to apply the formulation to the skin, significant transdermal penetration of progesterone was observed. By about 2 hours, serum progesterone increased about 10-fold in subject #3, but increased insignificantly in subjects #1 and #2. At approximately three hours, all of the subjects showed increased progesterone levels. Concentrations increased throughout the 8-9 hour experiment. There was no indication that either steady state or maximal serum levels had been reached.

Salivary progesterone levels also rose in a time dependent fashion, though the increases tended to lag those seen in the serum. Subjects #1 and #2 showed increases over basal of 60 and 33 fold at 24 hours, respectively. Subject #3's salivary progesterone level measured 25 ng/ml at around 8 hours in a single determination, with a lower value of 0.13 at 24 hours.

Subjects #1 and #2 showed decreases in serum progesterone at about 24 hours, around 9 hours following patch removal, the same time that their saliva hormone concentration reached its highest value during the experiment. Both serum and salivary concentrations had decreased, but were still supernormal, at about 48 hours, 33 hours after discontinuing administration of the hormone. Subject #3 showed a decline in both serum and salivary concentrations at 24 hours; he was not tested at 48 hours.

### 6.5.4 DISCUSSION

The purpose of this study was to determine whether the transdermal formulation of natural progesterone of the present invention could provide a safe and effective method for the transdermal administration of natural progesterone to humans. Despite the short duration of the study and the relative crudeness of the patch, the formulation delivered significant amount of hormone without skin irritation or any other detectable adverse effects. The results suggest that the formulation has utility as a safe and effective device to deliver natural progesterone.

Each of the three subjects showed increases in the levels of both circulating and salivary progesterone. None appeared to reach steady state, so maximal transport rates could be significantly greater than observed. Subject #3 showed a very large salivary concentration at about eight hours, but this value could be spurious. Clearly, more extensive evaluation of the formulation would be needed before establishing any firm conclusions about progesterone delivery rates. Questions obviously remain as to levels of penetration that may have been accomplished if the system had remained on the skin for an extended period of time, i.e. 12 - 24 hours with serial saliva and serum samples being obtained during those intervals. Because of the simplicity of the vehicle for the formulation, the data suggest that the transdermal penetration of progesterone was predominantly dependent on the effects of the hydrogel polymer in combination with the butylurea transdermal enhancer with progesterone. It should also be noted that the salivary levels of unbound progesterone achieved using the transdermal system are considerably higher than the peak ranges achieved historically by oral micronized progesterone (upper limits of 0.5 nanograms per ml), as measured by Aeron Life Cycles.

The results of this study correlate well with the results of the accompanying *in vitro* study performed on human skin described in Section 6.4. In this study, a similar preparation showed progesterone penetration rates of 3.2 $\mu g/cm^2/hr$ through human skin samples. It is not possible, given the limits of the current data, to predict what steady state serum concentrations might be achieved with this preparation.

From the analysis of *in-vivo* studies performed on human male subjects using transdermal progesterone described above, the question obviously arises as to clinical

efficacy of progesterone in the female who is using transdermal progesterone in combination with estrogen in the menopause. The major issue is whether sufficient progesterone levels are being achieved to prevent the risk of endometrial hyperplasia and adenocarcinoma.

A study performed by Joel T. Hargrove, et al., Obstetrics and Gynecology, Volume 7, D3, #4, April 1989, was the first to report the use of Natural estrogen and progesterone in combination for the management of the post-menopausal patient. The study revealed that oral administration of micronized progesterone in a complex oil base resulted in predictable reproducible increases in serum progesterone concentrations in a dose-dependent fashion.

At the completion of the Hargrove study, all women on estrogen and natural progesterone had a thin endometrium with complete quiescence and atrophy. The mean level for serum progesterone at baseline in the study was under 1 nanogram per ml. The mean level of progesterone at 12 months was less than 3 nanograms per ml. This level was achieved by using a total of 200 mg of natural progesterone combined with estrogen in divided doses. The present study suggests that comparable levels of natural progesterone could be achieved using compositions of the present invention. If one compares this data to the *in-vivo* and *in-vitro* studies described herein, it can be seen that suitable equivalent blood and saliva levels were achieved in a relatively short period of time transdermally using the inventive composition.

It should also be noted that despite the short half-life of progesterone in the orally ingested medication used in the Hargrove study, adequate conversion of the endometrium was achieved. It is expected that transdermal delivery of progesterone using compositions of the present invention will result in sustained blood levels of progesterone, resulting in a more predictable endometrial response.

**Table 11**

**Serum Progesterone Data**

| *Patient 1* | | *Patient 2* | | *Patient 3* | |
|---|---|---|---|---|---|
| Time Point (hr) | Concentration (ng/ml) | Time Point (hr) | Concentration (ng/ml) | Time Point (hr) | Concentration (ng/ml) |
| 0:00 | 0.4 | 0:00 | 0.4 | 0:00 | 0.4 |
| 1:50 | 0.4 | 1:45 | 0.5 | 1:15 | 0.5 |
| 3:50 | 0.8 | 3:45 | 1 | 3:00 | 1 |
| 4:50 | 1.1 | 4:45 | 1.7 | 4:15 | 1.2 |
| 6:50 | 1 | 6:45 | 1.6 | 6:15 | 1.3 |
| 8:50 | 1.3 | 8:45 | 2.1 | 8:15 | 1.8 |
| | | | | | |
| 24 Hour | 1.1 | 24 Hour | 1.1 | 24 Hour | 0.9 |
| | | | | | |
| 48 Hour | 0.5 | 48 Hour | 0.6 | | |

**Table 12**

**Saliva Progesterone Data**

| *Patient 1* | | *Patient 2* | | *Patient 3* | |
|---|---|---|---|---|---|
| Time Point (hr) | concentration (ng/ml) | Time Point (hr) | Concentration (ng/ml) | Time Point (hr) | Concentration (ng/ml) |
| 0:00 | 0.04 | 0:00 | 0.04 | 0:00 | 0.02 |
| 1:45 | 0.04 | 1:45 | 0.17 | 1:15 | 0.48 |
| 3:45 | 0.02 | 3:45 | 0.16 | 3:15 | 1.09 |
| 4:45 | 0.04 | 4:45 | 0.07 | 4:15 | 0.21 |
| 6:45 | 0.04 | 6:45 | 2.24 | 6:15 | 1.53 |
| 8:45 | 0.04 | 8:45 | 0.66 | 8:15 | 24.62 |
| | | | | | |
| 24 Hour | 2.38 | 24 Hour | 1.33 | 24 Hour | 0.13 |
| | | | | | |
| 48 Hour | 0.16 | 48 Hour | 0.19 | | |

The present invention is not to be limited in scope by the specific embodiments and examples described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. A composition comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

2. The composition of claim 1 which further comprises a glycolic, alcoholic or oil-based additive selected from the group consisting of propylene glycol, glycerin, mineral oil, corn oil, bran oil, rice oil, soy oil, ethylene glycol, xylene, and ethyl alcohol.

3. The composition of claim 1 which further comprises pectin.

4. The composition of claim 1 consisting essentially of 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin.

5. The composition of claim 1 consisting essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben, sodium chloride and pectin.

6. The composition of claim 1 consisting essentially of about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

7. The composition of claim 1 which further comprises a drug.

8. The composition of claim 7 wherein the drug is selected from the group consisting of nicotine, nitroglycerin, albuterol, VERAPAMIL®, scopolamine, n-butylurea, fentanyl, morphine, butaconazole, acetylsalicylic acid, MINOXIDIL®,

lidocaine, racemic menthol, methyl salicylate, benzalkonium chloride, DEET®, phenobarbital, iodine, insulin, salicylic acid, nonoxynol -9, erythromycin, tetracycline, cephalosporins, and acetaminophen.

9. A hydrogel comprising water and a base mixture, said base mixture comprising: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

10. The hydrogel of claim 9 which further comprises a glycolic, alcoholic or oil-based additive selected from the group consisting of propylene glycol, glycerin, mineral oil, corn oil, bran oil, rice oil, soy oil, ethylene glycol, xylene, and ethyl alcohol.

11. The hydrogel of claim 9 which further comprises coloring, fragrance, or other pharmaceutically acceptable additives.

12. The hydrogel of claim 9 wherein said base mixture further comprises pectin.

13. The hydrogel of claim 9 wherein said base mixture consists essentially of 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin.

14. The hydrogel of claim 9 wherein said base mixture consists essentially of about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

15. The hydrogel of claim 9 which further comprises a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl or a lower alkyl having from 1 to 8 carbon atoms.

16. The hydrogel of claim 15 wherein R is a lower alkyl group selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl.

17. The hydrogel of claim 15 wherein said substituted urea is butylurea.

18. The hydrogel of claim 9 which further comprises a drug.

19. The hydrogel of claim 18 wherein the drug is selected from the group consisting of nicotine, nitroglycerin, albuterol, VERAPAMIL®, scopolamine, n-butylurea, fentanyl, morphine, butaconazole, acetylsalicylic acid, MINOXIDIL®, lidocaine, racemic menthol, methyl salicylate, benzalkonium chloride, DEET®, phenobarbital, iodine, insulin, salicylic acid, nonoxynol-9, erythromycin, tetracycline, cephalosporins, and acetaminophen.

20. A composition in the form of a dry powder, said dry powder comprising

(a) a drug; and

(b) a base mixture comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

21. A composition in the form of a paste, said paste comprising

(a) a drug;

(b) a glycolic, alcoholic or oil-based additive; and

(c) a base mixture comprising (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural

gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride.

22. The composition of claim 21 wherein said glycolic, alcoholic or oil-based additive is selected from the group consisting of propylene glycol, glycerin, mineral oil, corn oil, bran oil, rice oil, soy oil, ethylene glycol, xylene, and ethyl alcohol.

23. The composition of claim 20 or 21 wherein said drug is selected from the group consisting of nicotine, nitroglycerin, albuterol, VERAPAMIL®, scopolamine, n-butylurea, fentanyl, morphine, butaconazole, acetylsalicylic acid, MINOXIDIL®, lidocaine, racemic menthol, methyl salicylate, benzalkonium chloride, DEET®, phenobarbital, iodine, insulin, salicylic acid, nonoxynol-9, erythromycin, tetracycline, cephalosporins, and acetaminophen.

24. The composition of claim 1, 20 or 21 which further comprises a coloring, fragrance, or other pharmaceutically acceptable additive.

25. The composition of claim 20 or 21 wherein said base mixture further comprises pectin.

26. The composition of claim 1, 20 or 21 further comprising a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl or a lower alkyl having from 1 to 8 carbon atoms.

27. The composition of claim 26 wherein R is a lower alkyl group selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl.

28. The composition of claim 26 wherein said substituted urea is butylurea.

29. The composition of claim 20 or 21 wherein said base mixture consists essentially of 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin.

30. The composition of claim 20 or 21 wherein said base mixture consists essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben, sodium chloride and pectin.

31. The composition of claim 20 or 21 wherein said base mixture consists essentially of about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

32. The composition of claim 20 or 21 wherein said drug is a hormone selected from the group consisting of progesterone, progestin, estrogen and testosterone.

33. The composition of claim 20 or 21 wherein said drug is the hormone progesterone.

34. A composition comprising:

(a) a hydrogel comprising water and a base mixture, said base mixture comprising: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride;

(b) a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl or a lower alkyl having from 1 to 8 carbon atoms; and

(c) a drug.

35. The composition of claim 34 wherein the drug is a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing.

36. A composition comprising:

(a) a hydrogel comprising water and a base mixture, said base mixture comprising: (i) a gelling agent consisting of methylcellulose or at least one natural gum, or a mixture thereof; (ii) at least one natural gum; (iii) glucose; (iv) propylparaben; (v) methyl paraben; and (vi) sodium chloride;

(b) a substituted urea of the formula R-NH-CO-$NH_2$ wherein R is hydrogen, hydroxyl or a lower alkyl having from 1 to 8 carbon atoms; and

(c) a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing.

37. The composition of claim 36 which further comprises a glycolic, alcoholic or oil-based additive selected from the group consisting of propylene glycol, glycerin, mineral oil, corn oil, bran oil, rice oil, soy oil, ethylene glycol, xylene, and ethyl alcohol.

38. The composition of claim 36 which further comprises a coloring, fragrance, or other pharmaceutically acceptable additive.

39. The composition of claim 30 wherein said base mixture further comprises pectin.

40. The composition of claim 36 wherein said base mixture consists essentially of 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin.

41. The composition of claim 36 wherein said base mixture consists essentially of methyl cellulose, a natural gum selected from the xanthan and guar gums, glucose, propyl paraben, methyl paraben sodium chloride and pectin.

42. The composition of claim 36 wherein said base mixture consists essentially of about 63% methylcellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methyl paraben, about 3% pectin and about 1.5% sodium chloride.

43. The composition of claim 36 wherein R is a lower alkyl group selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl.

44. A composition consisting essentially of:

(a) 3-12% of a base mixture consisting essentially of: 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthin and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin;

(b) 0.5-15% by weight of a substituted urea of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl;

(c) 5-20% by weight of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% by weight water;

in which said base mixture and water form a hydrogel.

45. A composition consisting essentially of:

(a) about 9% by weight of a base mixture consisting essentially of: about 63% (by weight) methyl cellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methylparaben, about 1.5% sodium chloride and about 3% pectin;

(b) about 2% by weight of a substituted urea of the formula: R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl;

(c) about 10% by weight of progesterone;

(d) about 20% by weight propylene glycol; and

(e) 59% by weight water; in which said base mixture and water form a hydrogel.

46. A composition consisting essentially of:

(a) about 9% by weight of a base mixture consisting essentially of: about 63% (by weight) methyl cellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methylparaben, about 1.5% sodium chloride and about 3% pectin;

(b) about 2% by weight butylurea;

(c) about 10% by weight of progesterone;

(d) about 20% by weight propylene glycol; and

(e) about 59% by weight water;

in which said base mixture and water form a hydrogel.

47. A composition consisting essentially of:

(a) a base mixture consisting essentially of methyl cellulose, guar gum, glucose, propylparaben, methyl paraben, sodium chloride and pectin;

(b) butylurea

(c) progesterone

(d) propylene glycol; and

(e) water;

in which said base mixture and water from a hydrogel.

48. A kit for the transdermal delivery of a drug to a subject comprising:

(a) a watch or a watch-like device comprising:

(i) a watch-case having a front face and a back face, the back face of said watch-case having a recessed chamber; and

(ii) a band or strap affixed to said watch-case and capable of attaching said watch or watch-like device to a limb of a subject such that a wafer having a top face and a bottom face, when situated within said recessed chamber, can be maintained such that the bottom face of said wafer is held in contact with the skin of said limb; and

(b) at least one of said wafer, said wafer

(i) comprising a drug; and

(ii) being capable of being situated within said recessed chamber and being removable from said chamber.

49. A kit for the transdermal delivery of a drug to a subject comprising a watch or a watch-like device comprising:

(a) a watch-case having a front face and a back face;

(b) a band or strap affixed to said watch-case and capable of attaching said watch or watch-like device to a limb of a subject;

(c) at least one disc-shaped drug reservoir comprising:

(i) a recessed chamber;

(ii) a plurality of clips that are capable of attaching said reservoir to the back face of said watch-case, such that a wafer having a top face and a bottom face, when situated within said recessed chamber, can be maintained such the bottom face of said wafer is held in contact with the skin of said limb; and

(d) at least one of said wafer, said wafer

(i) comprising a drug, and

(ii) being capable of being situated within said recessed chamber and being removable from said chamber.

50. The kit of claim 49 wherein said reservoir further comprises a plurality of slots capable of having said band or strap threaded through said slots.

51. A kit for the transdermal delivery of a drug to a subject comprising:

(a) at least one disc-shaped drug reservoir comprising:

(i) a recessed chamber; and

(ii) a plurality of slots;

(b) a band or a strap

(i) capable of being affixed to said reservoir by threading said band or strap through the slots of said reservoir;

(ii) capable of attaching said reservoir to a limb of a subject such that a wafer having a top face and a bottom face, when situated within said recessed chamber, is maintained such the bottom face of said wafer is held in contact with the skin of said limb; and

(c) at least one of said wafer, said wafer

(i) comprising a drug, and

(ii) being capable of being situated within said recessed chamber and being removable from said chamber.

52. The kit of claim 51 wherein said reservoir further comprises a plurality of clips that are capable of attaching said reservoir to a back face of a watch-case.

53. A device for the transdermal delivery of a drug to a subject comprising a watch or a watch-like device comprising:

(a) a watch-case having a front and a back face, the back-face of said watch-case having a recessed chamber;

(b) a wafer having a top face and a bottom face and comprising a drug, said wafer being situated within said recessed chamber and being removable from recessed chamber; and

(c) a band or strap affixed to said watch-case and capable of attaching said watch or watch-like device to a limb of a subject such that said bottom face of said wafer is maintained in contact with the skin of said limb.

54. A device for the transdermal delivery of a drug to a subject comprising a watch, or a watch-like device comprising:

(a) a watch-case having a front face and a back face,

(b) a disc-shaped drug reservoir comprising:

(i) a recessed chamber;

(ii) a wafer having a top face and a bottom face and comprising a drug, said wafer capable of being contained within said recessed chamber; and

(iii) a plurality of clips that are capable of attaching said reservoir to the back face of said watch-case such that said bottom face of said wafer can be maintained in contact with the skin of a limb of a subject; and

(c) a band or strap affixed to said watch-case capable of attaching said watch or watch-like device to the limb of said subject such that said bottom face of said wafer is maintained in contact with the skin of said limb.

55. The device of claim 54 wherein said reservoir further comprises a plurality of slots capable of having said band or strap threaded through said slots.

56. A device for the transdermal delivery of a drug to a subject comprising:

(a) a disc-shaped drug reservoir comprising:

(i) a recessed chamber;

(ii) a wafer having a top face and a bottom face and comprising a drug, said wafer being contained within said recessed chamber;

(iii) a plurality of slots; and

(b) a band or a strap

(i) threaded through said slots and thereby affixed to said reservoir; and

(ii) capable of attaching said reservoir to a limb of a subject such that said bottom face of said wafer is maintained such the bottom face of said wafer is held in contact with the skin of said limb.

57. The device of claim 48 wherein said reservoir further comprises a plurality of clips that are capable of attaching said reservoir to the back face of a watch-case.

58. The kit of claim 48, 49 or 51 wherein said wafer comprises:

(a) 3-12% of a base mixture consisting essentially of: 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin;

(b) 0.5-15% by weight of a substituted urea of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl;

(c) 5-20% by weight of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% by weight water;

in which said base mixture and water form a hydrogel.

59. A kit according to claim 48, 49 or 51 wherein said wafer comprises:

(a) about 9% by weight of a base mixture consisting essentially of: about 63% (by weight) methyl cellulose, about 21% guar gum, about 5%

glucose, about 3.5% propylparaben, about 3% methylparaben, about 1.5% sodium chloride and about 3% pectin;

(b) about 2% by weight butylurea;

(c) about 10% by weight of natural progesterone;

(d) about 20% by weight propylene glycol; and

(e) about 59% by weight water;

in which said base mixture and water form a hydrogel.

60. The device of claim 53, 54 or 56 wherein said wafer comprises:

(a) 3-12% of a base mixture consisting essentially of: 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthan and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin;

(b) 0.5-15% by weight of a substituted urea of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl;

(c) 5-20% by weight of a hormone selected from the group consisting of progesterone, progestin, estrogen, and testosterone, or a mixture of any two or more of the foregoing;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% by weight water;

in which said base mixture and water form a hydrogel.

61. The device of claim 53, 54 or 56 wherein said wafer comprises:

(a) about 9% by weight of a base mixture consisting essentially of: about 63% (by weight) methyl cellulose, about 21% guar gum, about 5% glucose, about 3.5% propylparaben, about 3% methylparaben, about 1.5% sodium chloride and about 3% pectin;

(b) about 2% by weight butylurea;

(c) about 10% by weight of progesterone;

(d) about 20% by weight propylene glycol; and

(e) about 59% by weight water;

in which said base mixture and water form a hydrogel.

62. The kit of claim 48 wherein said watch-case comprises a fluid-filled or hydrogel cushion layer capable of being situated within said recessed chamber and against said top face of said wafer.

63. The kit of claim 49 or 51 wherein said drug reservoir further comprises a fluid-filled or hydrogel cushion layer capable of being situated within said recessed chamber and against said top face of said wafer.

64. The device of claim 53 wherein said watch-case comprises a fluid-filled or hydrogel cushion layer capable of being situated within said recessed chamber and against said top face of said wafer.

65. The device of claim 54 or 56 wherein said drug reservoir further comprises a fluid-filled or hydrogel cushion layer capable of being situated within said recessed chamber and against said top face of said wafer.

66. The kit of claim 48 wherein said recessed chamber of said watch case comprises a heating layer having a top face and a bottom face, said heating layer comprising a means for heating said wafer, the bottom face of said heating layer being situated against the top face of said wafer.

67. The kit of claim 66 wherein said recessed chamber of said watch case further comprises a permanent closed cell having a top face and a bottom face, the bottom face of said permanent closed cell being situated against the top face of said heating layer.

68. The kit of claim 49 or 51 wherein said recessed chamber of said drug reservoir comprises a heating layer having a top face and a bottom face, said heating layer comprising a means for heating said wafer, the bottom face of said heating layer being situated against the top face of said wafer.

69. The kit of claim 68 wherein said recessed chamber of said drug reservoir further comprises a permanent closed cell having a top face and a bottom face, the bottom face of said permanent closed cell being situated against the top face of said heating layer.

70. The device of claim 53 wherein said recessed chamber of said watch case comprises a heating layer having a top face and a bottom face, said heating layer comprising a means for heating said wafer, the bottom face of said heating layer being situated against the top face of said wafer.

71. The device of claim 69 wherein said recessed chamber of said watch case further comprises a permanent closed cell having a top face and a bottom face, the bottom face of said permanent closed cell being situated against the top face of said heating layer.

72. The device of claim 54 or 56 wherein said recessed chamber of said drug reservoir comprises a heating layer having a top face and a bottom face, said heating layer comprising a means for heating said wafer, the bottom face of said heating layer being situated against the top face of said wafer.

73. The device of claim 71 wherein said recessed chamber of said drug reservoir further comprises a permanent closed cell having a top face and a bottom face, the bottom face of said permanent closed cell being situated against the top face of said heating layer.

74. A device for the transdermal delivery of a drug comprising a band or a strap having a surface which is coated with a composition of claim 7 or 36, wherein said band or strap is capable of being attached to a limb of a subject such that the surface of said band or strap is maintained in contact with the skin of said limb.

75. A device for the transdermal delivery of a drug to a subject comprising a glove wherein the inside of said glove is lined with a layer consisting essentially of:

(a) 3-12% of a base mixture consisting essentially of: 50-80% (by weight) methyl cellulose, 15-25% of a natural gum selected from the xanthin and guar gums, 3-7% glucose, 2-3.5% propylparaben, 1.5-3% methylparaben, 1-3% sodium chloride and 0.75-3.5% pectin;

(b) 0.5-15% by weight of a substituted urea permeation enhancer of the formula R-NH-CO-$NH_2$, wherein R is hydrogen, hydroxyl or lower alkyl having from 1 to 8 carbon atoms selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl and octyl;

(c) 5-20% by weight of a drug;

(d) 0-20% by weight propylene glycol; and

(e) 20-80% by weight water; in which said base mixture and water form a hydrogel.

76. A method of treating or preventing a condition responsive to hormone replacement therapy comprising placing a composition of claim 36, 44, or 45, said composition comprising a therapeutically effective amount of said hormone or mixture of hormones, in contact with the skin of a subject in need of such treatment.

77. The method of claim 76 wherein said condition is selected from the group consisting of premenstrual syndrome, menopause, infertility, osteoporosis, dysfunctional bleeding, corpus luteum failure, senile vulvo-vaginitis, and hypogonadism.

78. A method of providing contraception to a male or female subject comprising placing a composition of claim 36, 44, or 45, said composition comprising a therapeutically effective amount of said hormone or mixture of hormones, in contact with the skin of a subject in need of contraception.

79. The method of claim 78 wherein said subject is female and said hormone or mixture of hormones is selected from the group consisting of progesterone, progestin, estrogen, and a mixture of any two or more of the foregoing.

80. The method of claim 79 wherein said hormone is a mixture of one or more estrogens and one or more progestins.

81. The method of claim 79 wherein said hormone is a mixture of progesterone and one or more estrogens.

82. The method of claim 79 wherein said hormone is selected from the group consisting of progesterone and progestins.

83. The method of claim 78 wherein said subject is a male and said hormone is testosterone.

84. A method of delivering a therapeutically effective amount of a hormone or mixture of hormones to the bloodstream of a subject comprising contacting the skin of said subject with a composition of claim 36, 44, or 45 comprising a therapeutically effective amount of said hormone or mixture of hormones.

85. The method of claim 76 wherein said hormone is selected from the group consisting of progesterone, progestin, estrogen, testosterone and a mixture of any two or more of the foregoing.

86. The method of claim 76 wherein said hormone is natural progesterone.

87. The method of claim 76 wherein said hormone is a progestin selected from the group consisting of medroxy progesterone acetate, norethindrone, norethindrone acetate, norgestrel, ethynodiol diacetate and mixtures thereof.

88. The method of claim 76 wherein said hormone is an estrogen selected from the group consisting of 17-β-estradiol, diethylstilbestrol, estropipate, estrone estriol and mixtures thereof.

89. The method of claim 76 wherein said hormone is a mixture of a progestin selected from the group consisting of natural progesterone, medroxy progesterone acetate, norethindrone, norethindrone acetate, norgestrel, ethynodiol diacetate and mixtures thereof; and an estrogen selected from the group consisting of 17-β-estradiol, diethylstilbestrol, estropipate, estrone, estriol, and mixtures thereof.

90. The method of claim 76 wherein said hormone is testosterone.

91. A method for treating vaginal yeast infection comprising placing a composition of claim 7, 34, 36, 44 or 45 inside the vagina of a female subject suffering from yeast infection.

92. A method for providing contraception to a female subject comprising placing a composition of claim 7, 34, 36, 44 or 45 inside the vagina of a female subject in need of contraception.

93. A method for treating vaginal dryness comprising placing a composition of claim 7, 34, 36 44 or 45 inside the vagina of a female subject suffering from vaginal dryness.

94. A method for vaginal delivery of a drug comprising placing a composition of claim 7, 24, 36, 44 or 45 inside the vagina of a female subject.

95. A composition comprising:

(a) a base mixture that when combined with water forms a hydrogel;

(b) a permeation enhancer selected from the group consisting of urea, hydroxyurea, and an alkylurea; and

(c) a hormone selected from the group consisting of progesterone, progestin, estrogen and testosterone, or a mixture of any two or more of the foregoing.

96. A composition comprising:

(a) a hydrogel;

(b) a permeation enhancer selected from the group consisting of urea, hydroxyurea, and an alkylurea; and

(c) a hormone selected from the group consisting of progesterone, progestin, estrogen and testosterone, or a mixture of any two or more of the foregoing.

97. The composition of claim 95 or 96 wherein the alkylurea is butylurea.

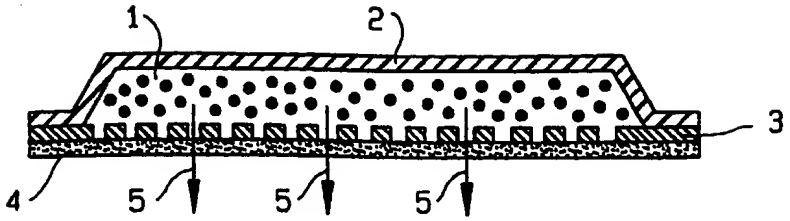


FIG. 1

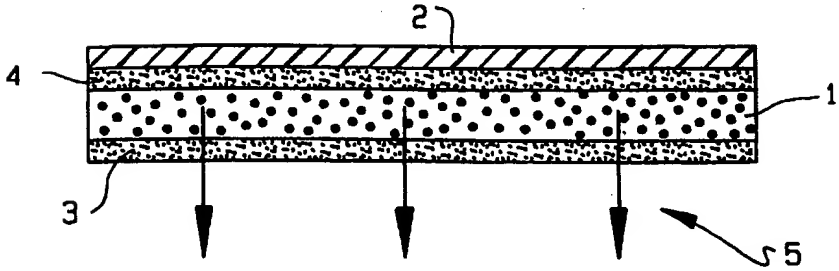


FIG. 2

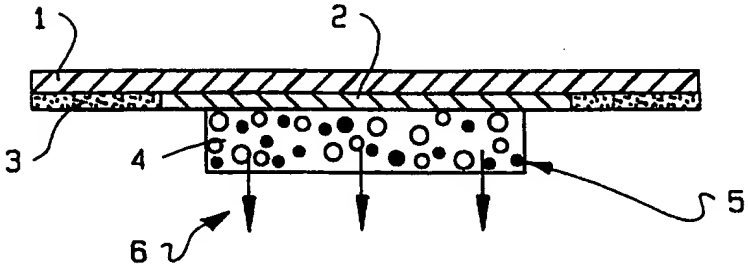


FIG. 3

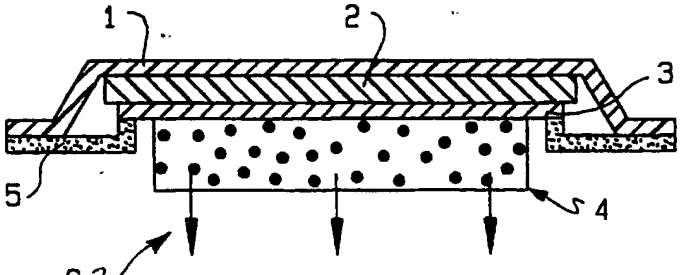


FIG. 4

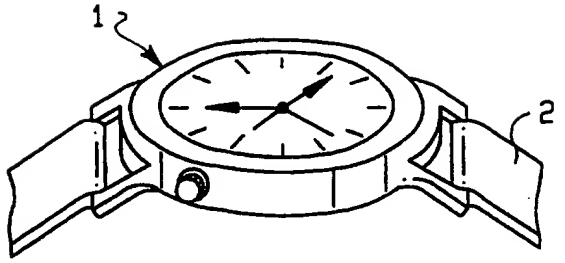


FIG. 5

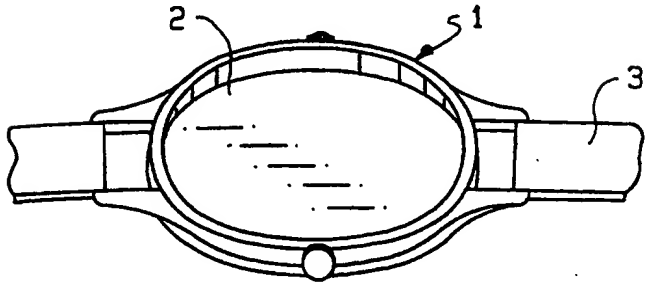


FIG. 6

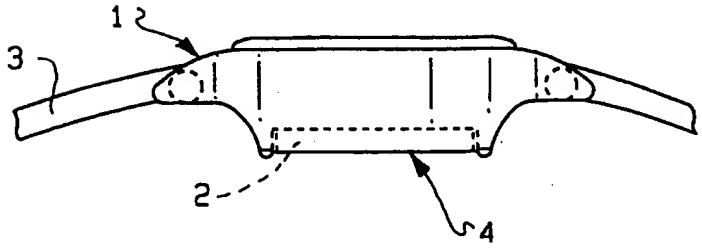


FIG. 7

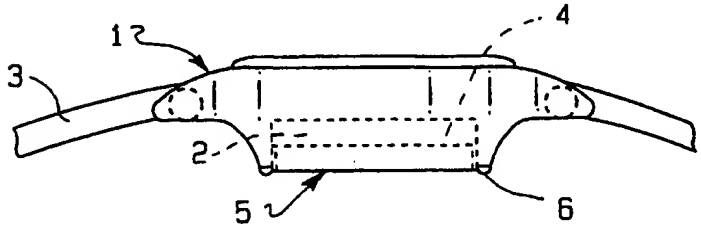


FIG. 8

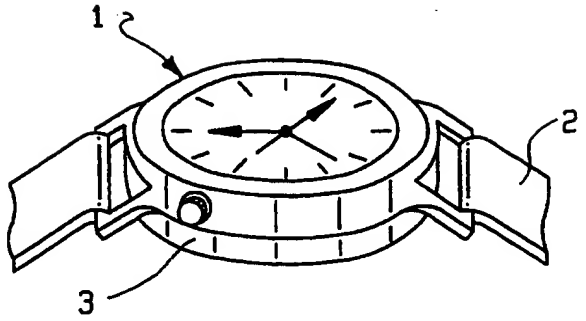


FIG. 9

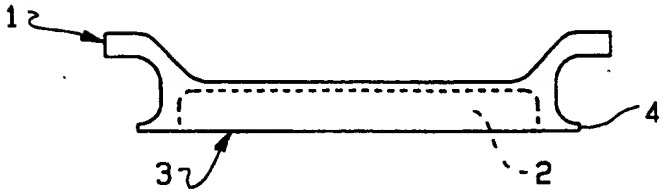


FIG. 10

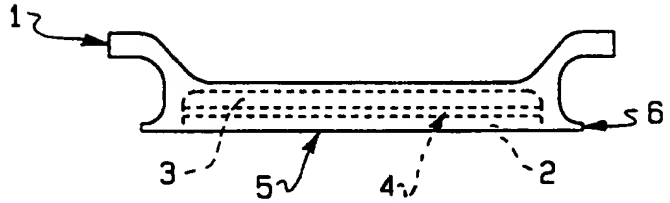


FIG. 11

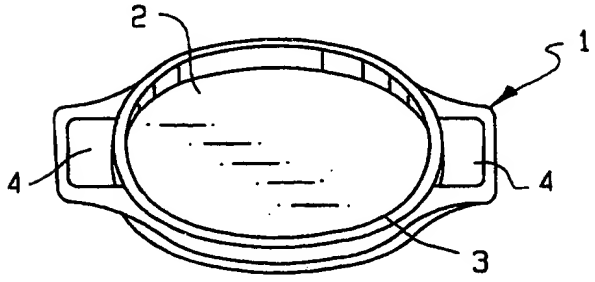


FIG. 12

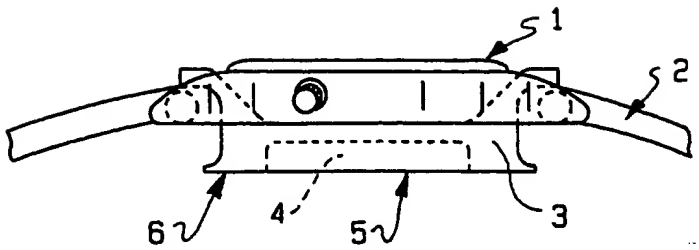


FIG. 13

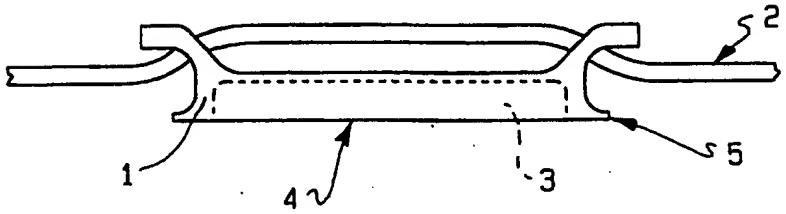


FIG. 14

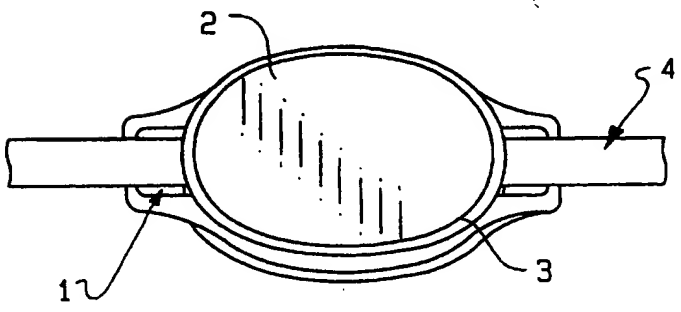


FIG. 15

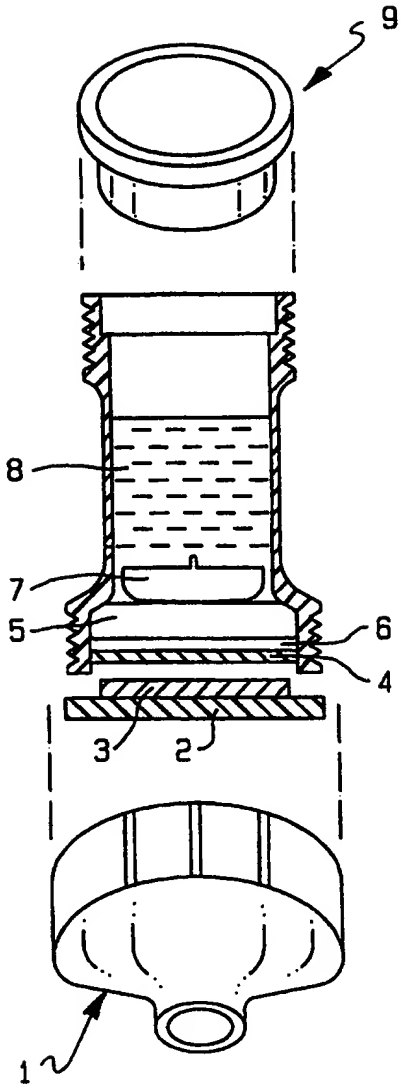


FIG. 16

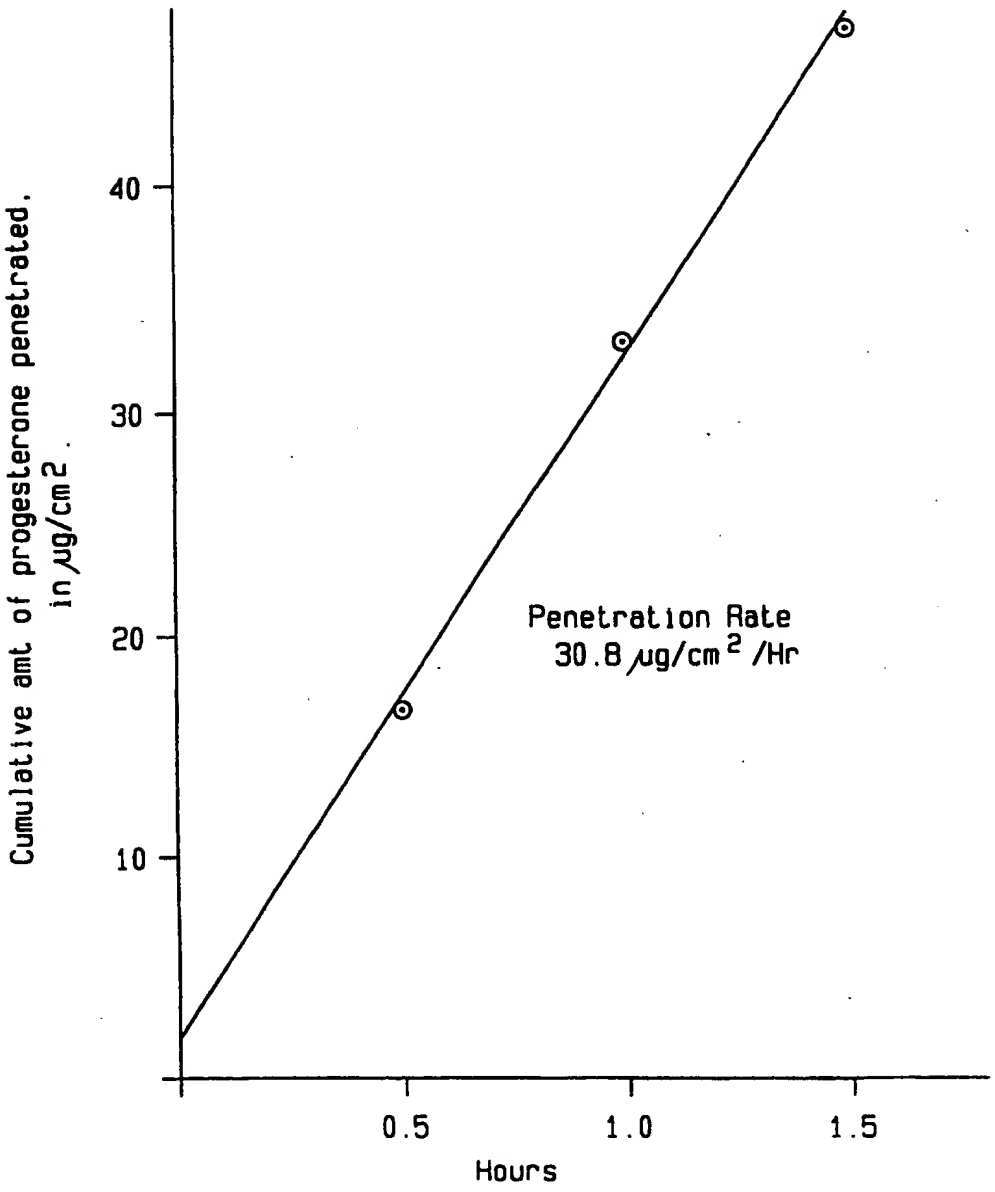
Cumulative amt of progesterone penetrated.
in µg/cm2.
40
30
20
10
Penetration Rate
30.8 µg/cm 2 /Hr
0.5
1.0
1.5
Hours

FIG. 17

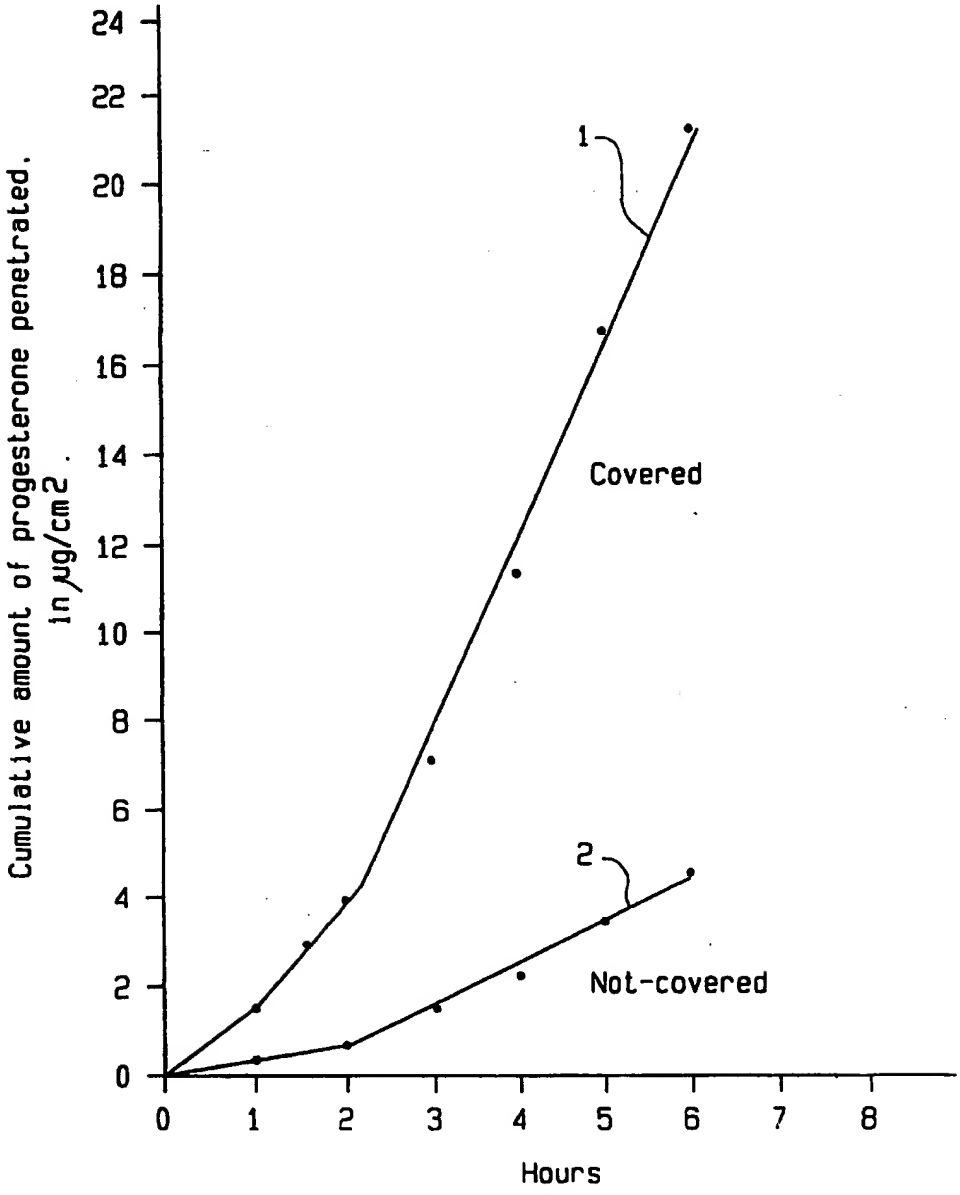
Cumulative amount of progesterone penetrated, in µg/cm2.
24
22
20
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
5
6
7
8
Hours
1
Covered
2
Not-covered

FIG. 18

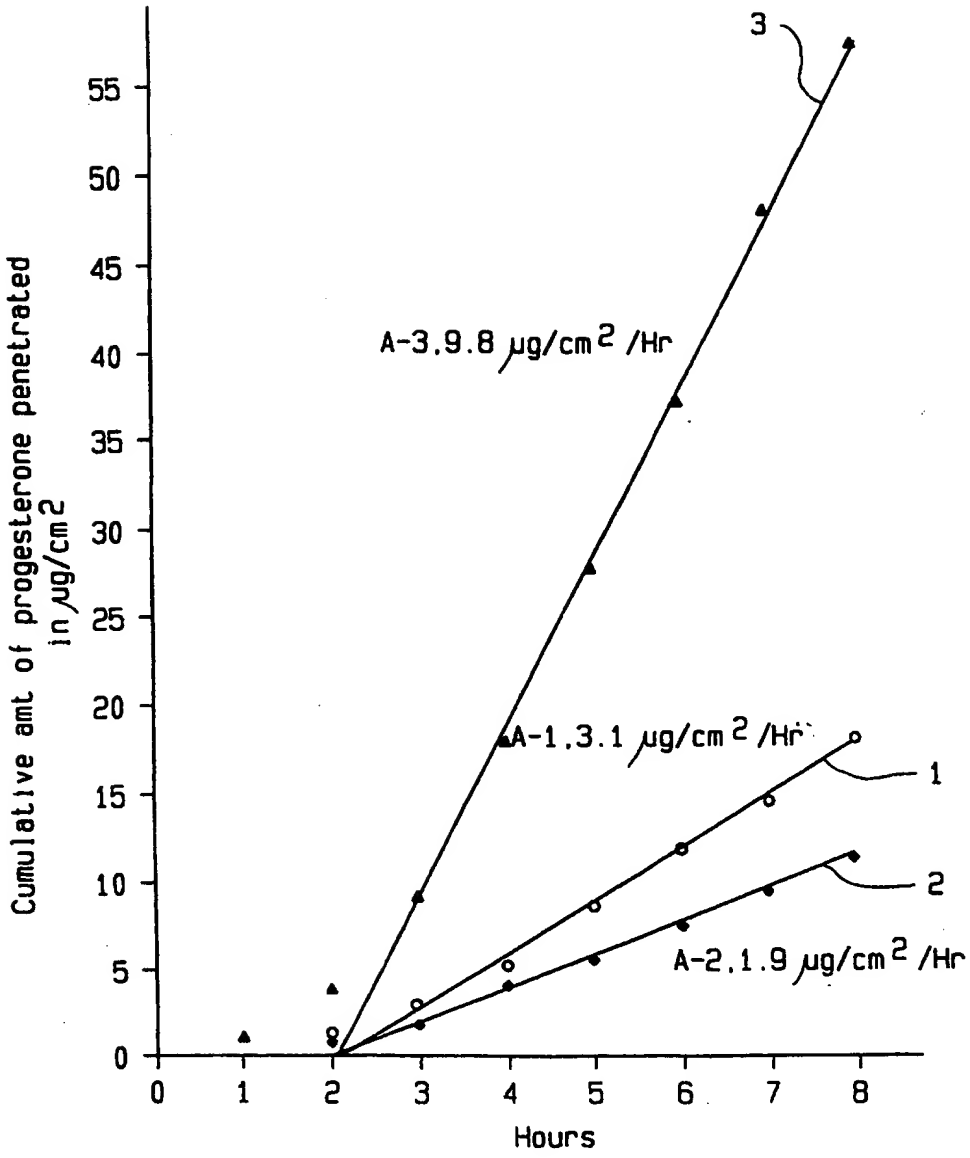
Cumulative amt of progesterone penetrated in µg/cm2
55
50
45
40
35
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
Hours
3
A-3.9.8 µg/cm2 /Hr
A-1.3.1 µg/cm2 /Hr
1
2
A-2.1.9 µg/cm2 /Hr

FIG. 19

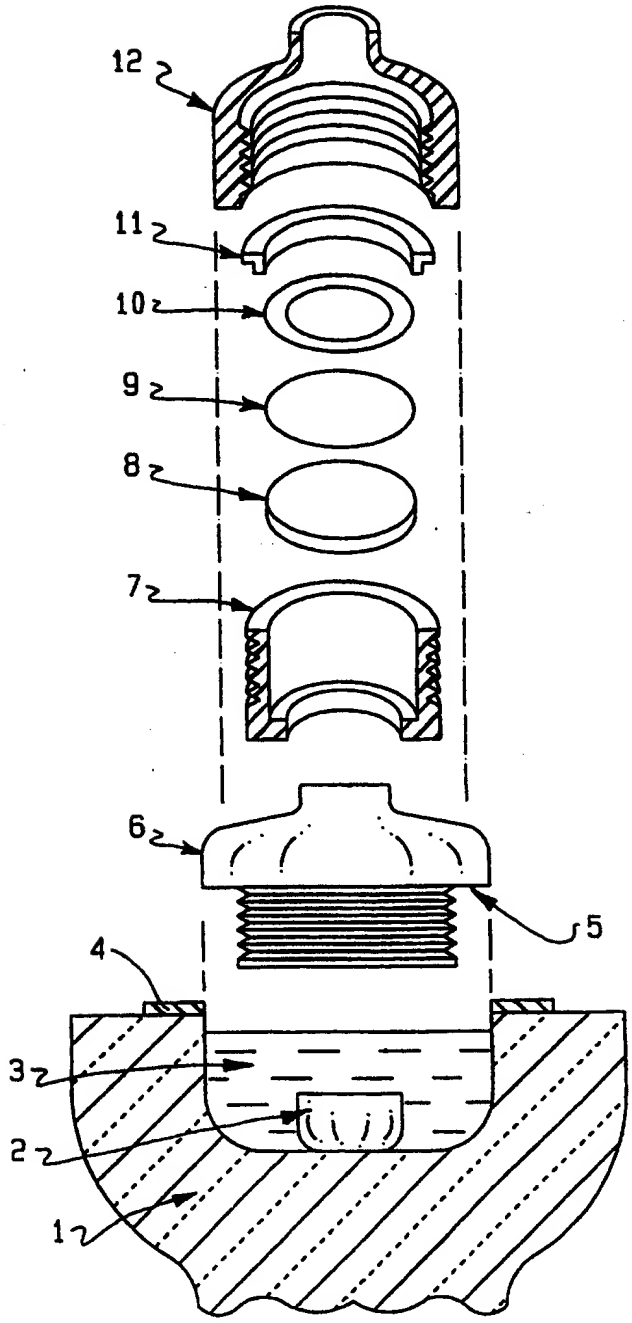


FIG. 20

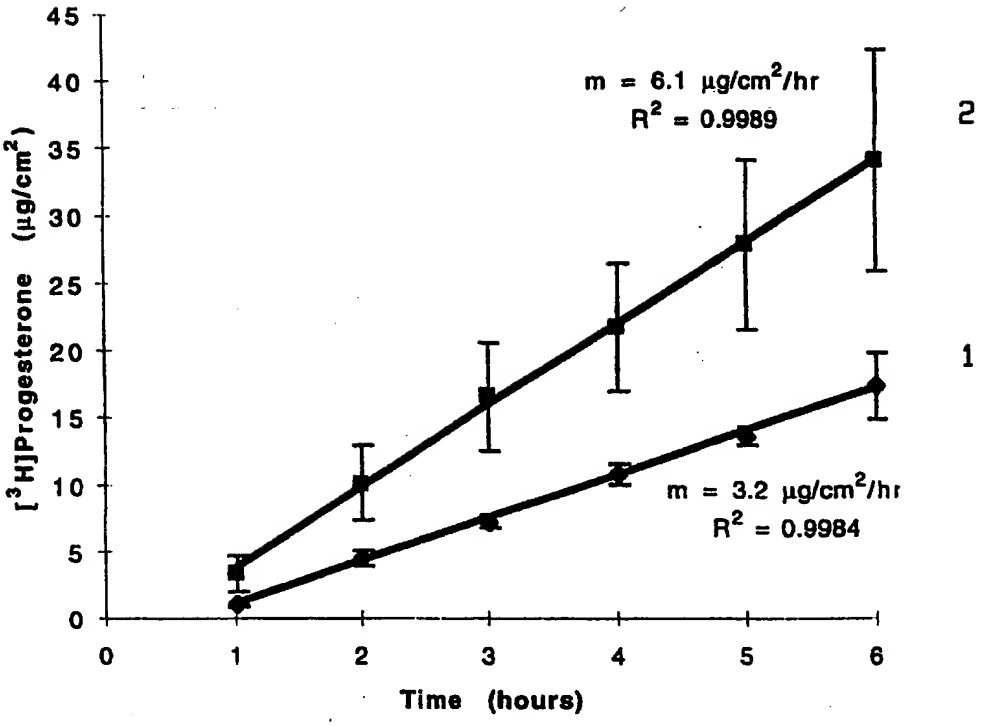
45
40
35
30
25
20
15
10
5
0
[3H]Progesterone (µg/cm2)
0
1
2
3
4
5
6
Time (hours)
m = 6.1 µg/cm2/hr
R2 = 0.9989
2
1
m = 3.2 µg/cm2/hr
R2 = 0.9984

FIG. 21

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08636

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61F 6/06, 13/00; A61K 9/66, 9/14
US CL :424/430, 443, 455, 484

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/430, 443, 455, 484

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

aps

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 5,232,705 A (WONG et al) 03 August 1993, column 3, lines 37-60; column 5, lines 49-51, 57; column 7, lines 34, 61; column 10, lines 57, 58; column 12, lines 22, 29, 40, 54; column 13, lines 37-38; column 14, line 17. | 1-97 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>14 JULY 1997 | Date of mailing of the international search report<br>21 AUG 1997 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>KATHRYNE E. SHELBORNE<br>Telephone No. (703) 308-2351 |

Form PCT/ISA/210 (second sheet)(July 1992)*